CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74587

Trade Name Verapamil Hydrochloride Extended-Release Tablets 240mg

Generic Name Verapamil Hydrochloride Extended-Release Tablets 240mg

Sponsor Mylan Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74587

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74587

APPROVAL LETTER

DIV

ANDA 74-587

Mylan Pharmaceuticals, Inc.
Attention: W. Bradley McMillen
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated December 12, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Verapamil Hydrochloride Extended-release Tablets, 240 mg.

Reference is also made to your amendments dated September 22, 1995, December 8, 1995 and February 26, 1996 and to your correspondence dated February 16, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Verapamil Hydrochloride Extended-release Tablets 240 mg, to be bioequivalent and, therefore therapeutically equivalent, to those of the listed drug (Isoptin® SR Tablets, 240 mg of Knoll Pharmaceutical Company).

Your dissolution testing should be incorporated into the stability and quality control program using the same method as proposed in your application and as outlined in our February 12, 1996 correspondence. The "interim" dissolution test(s) and tolerances are:

1 hour:
2 hours:
3.5 hours:
5 hours:
8 hours:

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches in a supplemental application. The supplemental application should be submitted under 21 CFR 314.70 (c)(1) when there are no revisions to the interim specifications or when the final specifications are tighter than the interim specifications. In all other instances the supplement should be submitted under 21 CFR 314.70 (b)(2)(ii).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application requires an approved supplemental application before the changes may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

Douglas L. Sporn
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74587

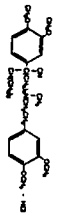
FINAL PRINTED LABELING

VERAPAMIL HYDROCHLORIDE

Extended-Release Oral Tablets
240 mg

DESCRIPTION: Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist). The tablets are designed for extended release of the drug in the gastrointestinal tract; extended release characteristics are not altered when the tablet is divided in half.

The structural formula of verapamil hydrochloride is given below:



$C_{27}H_{38}N_2O_4 \cdot HCl$ M.W. = 491.07

Benzeneacetonitrile,
α- [3-[[2-(3,4-dimethoxyphenyl) ethyl] methylamino]
propyl]-3,4-dimethoxy-α-(1-methylethyl) hydrochloride

Verapamil hydrochloride is an almost white, crystalline powder, practically free of odor, with a bitter taste. It is soluble in water, chloroform and methanol. Verapamil hydrochloride is not chemically related to other cardioactive drugs.

Each extended release tablet, for oral administration, contains 240 mg of verapamil hydrochloride. In addition, each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, sodium alginate, sodium lauryl sulfate, titanium dioxide, triacetin, and FD&C Blue #1 Aluminum Lake.

CLINICAL PHARMACOLOGY: Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Mechanism Of Action: *Essential Hypertension:* Verapamil exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats/min) is uncommon (1.4%). During isometric or dynamic exercise verapamil does not alter systolic cardiac function in patients with normal ventricular function.

Verapamil does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may alter the therapeutic effect of verapamil.

Other pharmacologic actions of verapamil hydrochloride include the following: Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at

normal ventricular function.

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Other pharmacologic actions of verapamil hydrochloride include the following: Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilization. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Verapamil regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

Electrical activity through the AV node depends, to a significant degree, upon calcium influx through the slow channel. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner.

Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus-node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without preexisting conduction defects (see WARNINGS).

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization, and conduction in depressed atrial fibers. Verapamil may shorten the antegrade effective refractory period of accessory bypass tracts. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see WARNINGS).

Verapamil has a local anesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in man.

Pharmacokinetics and Metabolism: With the immediate release formulation, more than 90% of the orally administered dose of verapamil hydrochloride is absorbed. Because of rapid biotransformation of verapamil during its first pass through the portal circulation, bioavailability ranges from 20% to 35%. Peak plasma concentrations are reached between 1 and 2 hours after oral administration. Chronic oral administration of 120 mg of verapamil hydrochloride every 6 hours resulted in plasma levels of verapamil ranging from 125 to 400 ng/mL, with higher values reported occasionally. A nonlinear correlation between the verapamil dose administered and verapamil plasma levels does exist. In early dose titration with verapamil a relationship exists between verapamil plasma concentration and prolongation of the PR interval. However, during chronic administration this relationship may disappear. The mean elimination half-life in single-dose studies ranged from 2.8 to 7.4 hours. In these same studies, after repetitive dosing, the half-life increased to a range from 4.5 to 12 hours (after less than 10 consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration. No relationship has been established between the plasma concentration of verapamil and a reduction in blood pressure.

Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly. In multiple dose studies under fasting conditions, the bioavailability measured by AUC of verapamil hydrochloride extended-release tablets was similar to verapamil hydrochloride immediate-release tablets; rates of absorption were, of course, different.

In a randomized, single-dose, crossover study using healthy volunteers, administration of verapamil hydrochloride extended-release tablets with food produced lower peak concentrations, delayed time to peak, and lesser total absorption (AUC), than when the product was administered to fasting subjects. Similar results were demonstrated for plasma norverapamil. Food thus produces decreased bioavailability (AUC) but a narrower peak-to-trough ratio. Good correlation of dose and response is not available, but controlled studies of extended-release verapamil have shown effectiveness of doses similar to the effective doses of its immediate release verapamil product.

In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in

effective doses of its immediate release verapamil product.

In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma; all except norverapamil are present in trace amounts only. Norverapamil can reach steady-state plasma concentrations approximately equal to those of verapamil itself. The cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. Approximately 90% is bound to plasma proteins. In patients with hepatic insufficiency, metabolism of immediate-release verapamil is delayed and elimination half-life prolonged up to 14 to 16 hours (see PRECAUTIONS); the volume of distribution is increased and plasma clearance reduced to about 30% of normal. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one-third of the oral daily dose required for patients with normal liver function.

After four weeks of oral dosing (120 mg q.i.d.), verapamil and norverapamil levels were noted in the cerebrospinal fluid with estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

Hemodynamics and Myocardial Metabolism: Verapamil reduces afterload and myocardial contractility. Improved left ventricular diastolic function in patients with HCSS and those with coronary heart disease has also been observed with verapamil hydrochloride. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload, and cardiac index is usually not reduced. However, in patients with severe left ventricular dysfunction, (e.g., pulmonary wedge pressure above 20 mmHg or ejection fraction less than 30%), or in patients taking beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may occur (see Drug Interactions).

Pulmonary Function: Verapamil does not induce bronchoconstriction and hence, does not impair ventilatory function.

INDICATIONS AND USAGE: Verapamil hydrochloride extended-release tablets are indicated for the management of essential hypertension.

CONTRAINDICATIONS: Verapamil hydrochloride is contraindicated in:

1. Severe left ventricular dysfunction (see WARNINGS).
2. Hypotension (systolic pressure less than 90 mmHg) or cardiogenic shock.
3. Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker).
4. Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker).
5. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g., Wolff-Parkinson-White, Lown-Ganong-Levine syndromes). (See WARNINGS.)
6. Patients with known hypersensitivity to verapamil hydrochloride.

WARNINGS: Heart Failure: Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4,954 patients, 87 (1.8%) developed congestive heart failure or pulmonary edema. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction less than 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see Drug Interactions). Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment. (Note interactions with digoxin under: PRECAUTIONS.)

Hypotension: Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4,954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60 degrees) was not able to induce orthostatic hypotension.

Elevated Liver Enzymes: Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even in the face of continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge; half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT, SGPT, and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine): Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, [illegible] rapid ventricular re-

2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt-table testing (60 degrees) was not able to induce orthostatic hypotension.

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Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine): Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see CONTRAINDICATIONS). Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil hydrochloride.

Atrioventricular Block: The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil hydrochloride and institution of appropriate therapy, depending upon the clinical situation.

Patients with Hypertrophic Cardiomyopathy (IHSS): In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension; abnormally high (greater than 20 mmHg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see Drug Interactions) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree AV block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, and only rarely did verapamil use have to be discontinued.

PRECAUTIONS: General: ***Use in Patients with Impaired Hepatic Function:*** Since verapamil is highly metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see OVERDOSAGE) should be carried out.

Use in Patients with Attenuated (Decreased) Neuromuscular Transmission: It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in Patients with Impaired Renal Function: About 70% of an administered dose of verapamil is excreted as metabo-

lites in the urine. Verapamil is not removed by hemodialysis. Until further data are available, verapamil should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see OVERDOSAGE).

Drug Interactions: ***Beta Blockers*** Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. The combination of extended-release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

A decrease in metoprolol and propranolol clearance has been observed when either drug is administered concomitantly with verapamil. A variable effect has been seen when verapamil and atenolol were given together.

Digitalis: Clinical use of verapamil in digitalized patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. However, chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29%, respectively. Maintenance digitalis doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over- or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil hydrochloride use, the patient should be reassessed to avoid underdigitalization.

Antihypertensive Agents: Verapamil administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

Antiarrhythmic Agents

Disopyramide: Until data on possible interactions between verapamil and disopyramide phosphate are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide: A study in healthy volunteers showed that the concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy (IHSS), concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should probably be avoided.

The electrophysiological effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

Other

Nitrates: Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Cimetidine: The interaction between cimetidine and clinically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

Lithium: Increased sensitivity to the effects of lithium (neurotoxicity) has been reported during concomitant verapamil–lithium therapy with either no change or an increase in serum lithium levels. However, the addition of verapamil has also resulted in the lowering of serum lithium levels in patients receiving chronic stable oral lithium. Patients receiving both drugs must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may

during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Rifampin: Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Cyclosporin: Verapamil therapy may increase serum levels of cyclosporin.

Theophylline: Verapamil may exhibit the clearance and increase the plasma levels of theophylline.

Inhalation Anesthetics: Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarization). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility: An 18-month toxicity study in rats, at a low multiple (6-fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35, and 120 mg/kg/day or approximately 1, 3.5, and 12 times respectively, the maximum recommended human daily dose (480 mg per day or 9.6 mg/kg/day).

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation.

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

Pregnancy: Pregnancy Category C. Reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively, and have revealed no evidence of teratogenicity. In the rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in the reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

Labor and Delivery: It is not known whether the use of verapamil during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labor.

Nursing Mothers: Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

Pediatric Use: Safety and efficacy of verapamil hydrochloride in pediatric patients below the age of 18 years have not been established.

Animal Pharmacology and/or Animal Toxicology: In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater, and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not in the rat. Development of cataracts due to verapamil has not been reported in man.

ADVERSE REACTIONS: Serious adverse reactions are uncommon when verapamil therapy is initiated with upward dose titration within the recommended single and total daily dose. See WARNINGS for discussion of heart failure, hypotension, elevated liver enzymes, AV block, and rapid ventricular response. Reversible (upon discontinuation of verapamil) non-obstructive, paralytic ileus has been infrequently reported in association with the use of verapamil. The following reactions to orally administered verapamil occurred at rates greater than 1% or occurred at lower rates but appeared clearly drug-related in clinical trials in 4,954 patients.

Constipation	7.3%
Dizziness	3.3%
Nausea	2.7%
Hypotension	2.5%
Headache	2.2%
Edema	1.9%
CHF/Pulmonary Edema	1.8%
Fatigue	1.7%
Dyspnea	1.4%
Bradycardia (HR<50/min)	1.4%
AV Block-total (1°, 2°, 3°)	1.2%
2° and 3°	0.8%
Rash	1.2%
Flushing	0.6%
Elevated Liver Enzymes (see WARNINGS)	

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Rash	1.2%
Flushing	0.6%
Elevated Liver Enzymes (see WARNINGS)	

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or flutter, ventricular rates below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

The following reactions, reported in 1% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship.

Cardiovascular: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

Digestive System: diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia.

Hemic and Lymphatic: ecchymosis or bruising.

Nervous System: cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence.

Skin: arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.

Special Senses: blurred vision.

Urogenital: gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

Treatment of Acute Cardiovascular Adverse Reactions: The frequency of cardiovascular adverse reactions that require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occurs following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g., intravenously administered norepinephrine bitartrate, atropine sulfate, isoproterenol HCl (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine HCl, metaraminol bitartrate, or methoxamine HCl) should be used to maintain blood pressure, and isoproterenol and norepinephrine should be avoided. If further support is necessary, dopamine HCl or dobutamine HCl may be administered. Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

OVERDOSAGE: Treat all verapamil overdoses as serious and maintain observation for at least 48 hours (especially extended-release verapamil hydrochloride), preferably under continuous hospital care. Delayed pharmacodynamic consequences may occur with the extended-release formulation. Verapamil is known to decrease gastrointestinal transit time.

Treatment of overdosage should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdosage with verapamil. Verapamil cannot be removed by hemodialysis. Clinically significant hypotensive reactions or high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

DOSAGE AND ADMINISTRATION: Essential Hypertension: The dose of verapamil should be individualized by titration and the drug should be administered with food. Initiate therapy with 180 mg of verapamil hydrochloride extended-release tablets given in the morning. Lower initial doses of 120 mg a day may be warranted in patients who may have an increased response to verapamil (e.g., the elderly or small people). Upward titration should be based on therapeutic efficacy and safety evaluated weekly and approximately 24 hours after the previous dose. The antihypertensive effects of verapamil hydrochloride extended-release tablets are evident within the first week of therapy.

If adequate response is not obtained with 180 mg of verapamil hydrochloride extended-release tablets, the dose may be titrated upward in the following manner:

a) 240 mg each morning,
b) 180 mg each morning plus 180 mg each evening; or 240 mg each morning plus 120 mg each evening
c) 240 mg every twelve hours.

When switching from verapamil hydrochloride immediate-release tablets to verapamil hydrochloride extended-release tablets, the total daily dose in milligrams may remain the same.

HOW SUPPLIED: Verapamil hydrochloride extended-release 240 mg tablets are supplied as blue, modified capsule-

morning plus 120 mg each evening

c) 240 mg every twelve hours.

When switching from verapamil hydrochloride immediate-release tablets to verapamil hydrochloride extended-release tablets, the total daily dose in milligrams may remain the same.

HOW SUPPLIED: Verapamil hydrochloride extended-release 240 mg tablets are supplied as blue, modified capsule shaped, scored, film-coated tablets containing 240 mg of verapamil hydrochloride. The tablet is debossed with M411 on one side and is blank on the reverse side.

They are available as follows:

NDC 0378-0411-01
bottles of 100 tablets
NDC 0378-0411-05
bottles of 500 tablets

STORE BETWEEN 15° AND 25°C (59° AND 77°F).

PROTECT FROM LIGHT AND MOISTURE.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED FEBRUARY 1996
VERER-R2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74587

CHEMISTRY REVIEW(S)

9.1

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-587

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals, Inc.
Attention: Patrick K. Noonan, Ph.D.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. BASIS OF SUBMISSION
Knoll Pharmaceutical - Isoptin® SR Tablets

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Verapamil Hydrochloride
Extended-release tablet

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:
Submitted: December 12, 1994
New Correspondence (Form 356h): December 20, 1994
Amendment: June 27, 1995
Amendment (Bio): September 22, 1995
Amendment (Label): December 8, 1995
New Correspondence (Bio): February 16, 1996
Amendment (Chemistry/label): February 26, 1996
(Item in bold subject of Review # 3)

FDA:
Acknowledgement: January 6, 1995
Letter; C.R. #1: May 12, 1995
Bio letter & review: August 22, 1995
Bio letter (Bio specifications): February 12, 1996
Letter, C.R #2: February 16, 1996

10. PHARMACOLOGICAL CATEGORY
Calcium ion influx inhibitor

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

LOAs included

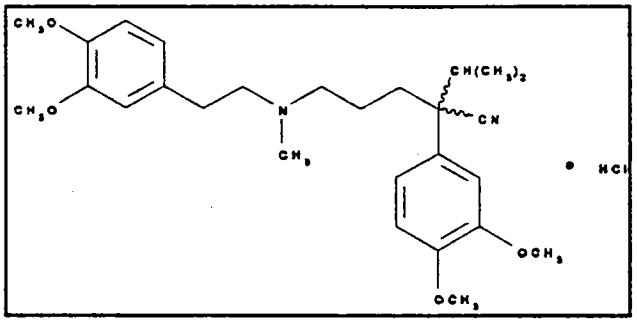
13. DOSAGE FORM
Tablet (Film coated, Extended-release

14. POTENCY
240 mg

15. CHEMICAL NAME AND STRUCTURE

Verapamil Hydrochloride USP

$C_{27}H_{38}N_2O_4.HCl$; M.W. = 491.07



(±)-5-[(3,4-Dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile monohydrochloride.
CAS [152-11-4]

16. RECORDS AND REPORTS: N/A

17. COMMENTS

a. CMC issues satisfactory.
b. EER acceptable 10/23/95 for all firms.
c. Bio satisfactory 2/2/96.
d. See item # 37 for DMF summary.
e. MV satisfactory.
f. Labeling satisfactory for approval 3/5/96.

18. CONCLUSIONS AND RECOMMENDATIONS
This ANDA can be approved.

19. REVIEWER:
Donald Shostak

DATE COMPLETED:
March 7, 1996

OCT 8 1996

Verapamil HCl ER Tablet
240 mg
ANDA #74-587
Reviewer: Moheb H. Makary
WP 74587D.596

Mylan Pharmaceuticals Inc
Morgantown, West Virginia
Submission Date:
May 17, 1996

Review of a Supplement

The firm submitted this supplement containing dissolution data on its currently approved Verapamil HCl ER 240 mg Tablets for the first three full-scale production lots of the above referenced product. The dissolution results (please see attachment) indicate that the "interim" dissolution specifications:

1 hour :
2 hours:
3.5 hours:
5 hours:
8 hours:

are appropriate to control Mylan's Verapamil HCl ER Tablets, 240 mg. The results conform to the specifications and acceptance criteria provided in <724> of the USP 23. The dissolution method and specifications were previously recommended to the firm by the Division of Bioequivalence on February 2, 1996 in response to the submission dated September 22, 1995. The firm indicated that the above specifications have already been implemented for both releasing and monitoring the stability of the finished product. Consequently, no further action is needed.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATR _____ ate: 10/7/96

Concur: _____ Date: 10/8/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/10-7-96 wp 74587D.596
cc: ANDA #74-587, original, HFD-658 (Makary), Drug File, Division File.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74587

BIOEQUIVALENCE REVIEW(S)

Verapamil HCl Extended Release Tablets, 240 mg
Summary of Dissolution Data

	1 hour Between	2 hours Between	3.5 hours Between	5 hours Between	8 hours NLT
Lot 2C009A					
Average	14.8%	20.9%	37.8%	55.4%	86.8%
Range					
Lot 2C010A	14.6%	21.3%	39.5%	58.0%	89.4%
Average					
Range					
Lot 2C011A	14.8%	21.2%	38.4%	56.4%	87.0%
Average					
Range					

* The averages and ranges listed above encompass the results from each pan representing 72 samples for each time point. Individual data may be found on the following pages.

DISSOLUTION DATA FOR
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG

FIRST PRODUCTION
SIZE BATCH MANUFACTURED
LOT 2C009A

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C009A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #1

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.9%	20.8%	37.6%	55.3%	87.9%
SD	0.3	0.6	1.8	3.3	5.0
RSD	2.1%	2.7%	4.7%	5.9%	5.7%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C009A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #2

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.7%	21.1%	35.4%	51.9%	83.2%
SD	0.4	1.8	2.7	3.0	4.5
RSD	3.0%	8.6%	7.6%	5.7%	5.4%
Range					

(RDLIB.ANDA.VERAPAMIL-ER-240)AGENCY-LETTER-DATED.032396

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C009A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #3

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	15.1%	21.5%	39.5%	60.0%	89.4%
SD	0.4	0.5	1.9	2.9	3.0
RSD	2.5%	2.5%	4.8%	4.9%	3.3%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C009A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #4

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.7%	20.9%	38.8%	55.3%	88.6%
SD	0.2	0.9	3.1	3.9	5.3
RSD	1.6%	4.5%	8.0%	7.1%	6.0%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C009A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #5

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.8%	20.8%	37.1%	55.5%	85.6%
SD	0.3	1.0	2.4	3.7	5.9
RSD	1.9%	4.6%	6.5%	6.7%	7.0%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C009A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #6

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.8%	20.4%	38.1%	54.6%	85.8%
SD	0.2	0.5	2.6	4.0	4.2
RSD	1.6%	2.3%	6.8%	7.3%	4.9%
Range					

DISSOLUTION DATA FOR
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG

SECOND PRODUCTION
SIZE BATCH MANUFACTURED
LOT 2C010A

DISSOLUTION OF VERAPAMIL HCl IN
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG
LOT #2C010A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #1

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.4%	20.9%	39.8%	59.8%	90.2%
SD	0.2	0.8	3.3	4.9	5.1
RSD	1.7%	3.8%	8.3%	8.1%	5.6%
Range					

DISSOLUTION OF VERAPAMIL HCl IN
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG
LOT #2C010A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #2

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.4%	21.1%	39.9%	58.7%	90.5%
SD	0.4	0.7	1.8	2.9	4.1
RSD	2.9%	3.5%	4.4%	5.0%	4.5%
Range					

DISSOLUTION OF VERAPAMIL HCl IN
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG
LOT #2C010A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #3

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.9%	21.7%	40.2%	58.8%	90.9%
SD	0.4	1.0	3.5	5.8	7.3
RSD	2.5%	4.5%	8.8%	9.9%	8.0%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C010A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #4

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.7%	21.1%	40.1%	59.0%	90.0%
SD	0.3	0.7	3.1	5.1	5.6
RSD	1.7%	3.1%	7.8%	8.7%	6.2%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C010A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #5

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.8%	21.4%	38.2%	56.1%	86.9%
SD	0.3	1.0	2.5	4.3	5.5
RSD	2.1%	4.9%	6.5%	7.6%	6.3%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C010A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #6

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.7%	21.4%	38.9%	55.8%	88.2%
SD	0.5	0.5	2.6	3.8	4.8
RSD	3.1%	2.6%	6.7%	6.9%	5.4%
Range					

FORM FDA 356h

BASIS FOR ANDA SUBMISSION

DISSOLUTION DATA FOR
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG

THIRD PRODUCTION
SIZE BATCH MANUFACTURED
LOT 2C011A

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C011A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #1

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.8%	21.0%	37.6%	54.2%	84.5%
SD	0.4	0.7	3.0	4.7	6.1
RSD	3.0%	3.3%	8.1%	8.6%	7.2%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C011A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #2

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.7%	20.9%	38.3%	56.1%	87.5%
SD	0.3	0.8	2.9	4.2	4.8
RSD	2.2%	3.6%	7.7%	7.6%	5.5%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C011A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #3

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.7%	21.0%	38.5%	57.2%	88.8%
SD	0.3	0.8	3.6	6.1	6.6
RSD	2.1%	3.7%	9.3%	10.7%	7.4%
Range					

DISSOLUTION OF VERAPAMIL HCl IN
VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG
LOT #2C011A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #4

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	15.0%	21.6%	39.2%	57.4%	86.3%
SD	0.4	0.8	3.0	5.6	7.6
RSD	2.5%	3.6%	7.8%	9.7%	8.8%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C011A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #5

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.9%	21.5%	38.2%	55.9%	86.8%
SD	0.4	0.6	1.3	3.0	5.6
RSD	2.5%	2.8%	3.4%	5.4%	6.5%
Range					

DISSOLUTION OF VERAPAMIL HCl IN VERAPAMIL HCl EXTENDED RELEASE TABLETS, 240 MG LOT #2C011A

Apparatus 2 (paddles) @ 50 rpm
900 mL of Simulated Gastric Fluid, TS (without enzymes) for the first hour
900 mL of Simulated Intestinal Fluid, TS (without enzymes) thereafter for seven additional hours

PAN #6

Time Acceptance Criteria	1 hour Between	2 hour Between	3.5 hour Between	5 hour Between	8 hour NLT
AVG	14.4%	21.4%	38.6%	57.3%	88.1%
SD	0.2	1.0	3.5	5.5	6.0
RSD	1.0%	4.8%	9.1%	9.6%	6.8%
Range					

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-587 SPONSOR: Mylan Pharmaceutical
DRUG: Verapamil Hcl
DOSAGE FORM: ER Tablets
STRENGTH(s): 240 mg
TYPE OF STUDY: Singie/Multiple Fasting/Fed
STUDY SITE:

STUDY SUMMARY: The three bioequivalence studies on Verapamil Hcl 240 mg extended release tablets are acceptable.

DISSOLUTION: The dissolution testing on the verapamil Hcl 240 mg ER tablets is acceptable. Waiver is granted for the

PRIMARY REVIEWER: BRANCH: III

INITIAL: DATE: 2/12/96

BRANCH CHIEF: BRANCH:

INITIAL DATE: 2/12/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DATE: 2/15/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: N/A DATE:

SEP 15 1997

Verapamil HCl ER Tablet
180 mg
ANDA #74-587
Reviewer: Moheb H. Makary
WP 74587SD.297

Mylan Pharmaceuticals Inc
Morgantown, West Virginia
Submission Date:
February 13, 1997

Review of a Bioequivalence Study and Dissolution Data

I. Objective:

The firm submitted a bioequivalence study under fasting conditions to assess the bioequivalence of the Mylan's Verapamil HCl Extended-release Tablet, 180 mg, to Knoll's Isoptin® SR 180 mg Tablet. Dissolution profiles comparing Mylan's Verapamil HCl Extended - release 180 mg tablets to Isoptin® tablets were submitted. Comparative compositions were also submitted.

The firm currently holds an approved ANDA #74-587 for Verapamil HCl Extended-release Tablets 240 mg since March 23, 1996.

The following study was performed and included in the submission:

Study #ISOP-9662
A two-way crossover, single-dose bioequivalence study on verapamil HCl 180 mg Extended-release (ER) tablets under fasting conditions.

II. Background:

Verapamil is a calcium-channel blocking agent. Its mechanism of action involves inhibition of ATP-dependent calcium transport properties of the sarcolemma and intrinsic calcium-sensitive ATPase. The drug is well absorbed orally (over 90%). However, extensive first-pass metabolism reduces absolute bioavailability to approximately 20%. An N-dealkylated metabolite, norverapamil, is active and upon single dose administration the AUC of this metabolite equals or exceeds that of the parent drug. The mean elimination half-life for verapamil in single dose studies ranged from 2.8 to 7.4 hours.
As an anti-anginal agent, the usual dose is 80-120 mg three times daily. As an anti-arrhythmic, the usual dose ranges from 240-320 mg or from 240-480 mg per day (in 3 or 4 divided doses). To treat essential hypertension, the usual initial dose for monotherapy is 80 mg three times daily, individualized to 360 mg daily.
Verapamil HCl is marketed as 80 and 120 mg conventional release tablets. The drug is also marketed as a 120 mg, 180 mg and 240 mg sustained release tablets for treatment of essential

hypertension. The usual daily dose is 240 mg once daily in the morning. Labeling describes higher doses if necessary. Labeling also indicates that the drug should be dosed with food.

III. Study #ISOP-9662 For Single-Dose, Two-Way Crossover On Verapamil HCl Extended-release Tablets, 180 mg, Under Fasting Conditions:

The objective of the study was to compare the bioavailability of verapamil-ER 180 mg tablets manufactured by Mylan Pharmaceuticals Inc., with that of Knoll product (Isoptin® SR), following an oral administration of a single 180 mg dose (1x180 mg tablet) of each product under fasting conditions.

Clinical site:

Analytical site:

Investigators:

Study design: Single-dose, two-way crossover bioequivalence study, under fasting conditions.

Subjects: Forty-seven (47) male subjects were accepted for entry into the clinical portion of the study. All (47) subjects successfully completed both phases of the clinical portion of the study. Group A consisted of volunteers 1-14, Group B consisted of volunteers 15-24 and Group C consisted of volunteers 25-47. The dosing dates for this study were as following:

	Phase I	Phase II
Group A	August 29	September 12, 1996
Group B	September 28	October 12, 1996
Group C	October 26	November 9, 1996

Selection criteria: The subjects were between 19 to 45 years of age. All subjects were within ±10% of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination, EKG and medical history within fourteen days of the start of the study. In addition, urine samples at the time of the medical examination were free of drug abuse (including marijuana). Good health was

	confirmed by normal findings in the following tests: biochemical profile, hematology and urinalysis.
Exclusion criteria:	Consisted of adverse reactions or allergy to verapamil or any other calcium channel blockers, history of alcohol or drug abuse, history of cardiovascular, neurological, neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases.
Restrictions:	Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. In addition, no concomitant medication was permitted during the study period. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine-containing products for 48 hours prior to, and during the course of the study.
Dose and treatment:	Treatment A: 1x180 mg Isoptin®SR tablet (Knoll), lot #21290016, Exp. 7/98, potency 99.1%, content uniformity 99.5% (CV=1.5%), administered following a 10 hours overnight fast. Treatment B: 1x180 mg verapamil HCl ER tablet (Mylan), lot #2B005H, batch size Tablets, potency 95.4%, content uniformity 95.1% (CV=2.0%), administered following a 10 hours overnight fast.
Washout period:	Two weeks
Food and fluid intake:	Subjects fasted for ten hours prior to dosing. Lunch was served five hours and dinner was served ten hours after dosing. Water was not allowed two hours before until two hours after dosing, except for the dosing water (240 mL).
Blood samples:	Ten mL (10) blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours after dosing. Plasma samples were immediately frozen.

Assay Methodology:

Subject welfare: Vital signs (blood pressure, pulse rate and Lead II ECG) were measured pre-dose and hourly for eight hours after dosing and at 12, 24, 36 and 48 hours.

Statistical Analysis:

Statistical analysis was performed on verapamil and norverapamil data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The subjects in the study were dosed in three separate groups. Group A consisted of subjects numbered 1 to 14, group B consisted subjects numbered 15 to 24 and group C consisted of subject numbered 25-47. An analysis of variance was performed to assess the group effect and determine the poolability of the three groups. A mode with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, treatments and periods was performed. No statistically significant group effects were observed for the pharmacokinetic parameters by using the above model. The firm dropped the group effect, and the standard two way crossover model was employed.

IV. In Vivo Results:

Forty-seven (47) normal, healthy subjects were recruited for the study and successfully completed both phases of the clinical portion of the study.
Twelve (12) adverse events [headache (11) and nausea (1)] were reported in nine subjects dosed over the course of the study. All the reported adverse events were probably or possibly related to the study drug.

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables I and II.

Table I

Mean Plasma Verapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 180 Verapamil HCl ER (1x180 mg Tablet) under Fasting Conditions

(N=47)

Time hr	Treatment A Reference Lot #21290016 ng/mL(CV)	Treatment B Mylan-Test Lot #2B005H ng/mL(CV)
0	0	0
0.5	0.42 (345)	0.53 (270)
1	6.55 (159)	8.05 (110)
1.5	15.70 (110)	18.60 (84.6)
2	26.90 (91.9)	31.40 (80.1)
2.5	38.40 (76.9)	48.40 (65.4)
3	48.40 (74.2)	61.70 (65.2)
4	58.30 (64.9)	68.60 (70.9)
5	61.40 (65.6)	65.00 (71.5)
6	77.80 (59.6)	63.80 (62.1)
7	61.90 (53.2)	52.40 (58.7)
8	53.60 (53.5)	44.50 (53.2)
10	38.30 (48.0)	33.70 (48.0)
12	28.40 (50.1)	27.10 (55.4)
16	18.50 (57.2)	16.90 (58.7)
24	11.80 (70.3)	9.72 (71.1)
36	3.14 (121)	2.39 (129)
48	0.94 (214)	0.56 (248)

			90% CI
AUC(0-t) (ng.hr/mL)	829.0 (49.7)	770.0 (47.8)	
AUCINf (ng.hr/mL)	904.0 (47.6)	840.0 (44.3)	
Cpeak(ng/mL)	85.0 (54.9)	84.5 (57.1)	
Tpeak (hr)	5.78	5.54	
Kel(1/hr)	0.092	0.098	
T1/2(hr)	8.15	7.78	
LnAUC(0-t)			85-101%
LnAUCI			85-101%
LnCpeak			87-112%

1. For verapamil, the means for AUC(0-t), AUCI and Cpeak values were 7.1%, 7.1% and 0.6% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The verapamil plasma levels peaked at 4 and 6 hours for the test and the reference products, respectively, following their administration under fasting conditions.

3. It should be noted that the firm used a statistical model to assess the group effect. The Division of Biometrics recommended using the following model:
Y = SEQ SUBJ(SEQ) PER TRT; (whereas period = 6)
Analysis of variance was performed by the reviewer using the above model, the resulting 90% confidence intervals for LnAUC(0-24) and LnCpeak were as following:

Verapamil	
LnAUC(0-t)	84.8-102.1%
LnAUCinf	84.8-101.2%
LnCpeak	87.3-111.8%
Norverapamil	
LnAUC(0-t)	89.0-100.1%
LnAUCinf	88.8-99.3%
LnCpeak	88.2-104.7%

All confidence intervals remained within the acceptable 80-125% range.

4. Systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval were analyzed for statistical differences. There were no clinically significant differences in the parameters evaluated.

Table II

Mean Plasma Norverapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 180 Verapamil HCl ER (1x180 mg Tablet) under Fasting Conditions
(N=47)

Time hr	Treatment A Reference Lot #21290016 ng/mL(CV)	Treatment B Mylan-Test Lot #2B005H ng/mL(CV)
0	0	0
0.5	0.12 (686)	0.06 (686)
1	3.69 (154)	5.17 (101)
1.5	11.30 (89.7)	13.70 (71.6)
2	19.90 (68.5)	23.70 (62.4)
2.5	28.70 (56.3)	34.90 (49.6)
3	36.80 (52.6)	44.90 (48.3)
4	48.10 (45.5)	54.50 (51.1)

5	53.40 (41.7)	57.40 (48.4)
6	63.80 (39.5)	59.20 (43.2)
7	60.60 (35.3)	56.50 (40.1)
8	58.40 (33.3)	54.20 (37.4)
10	50.60 (31.3)	46.70 (30.5)
12	41.90 (29.5)	40.00 (29.9)
16	31.50 (30.0)	29.60 (30.3)
24	21.60 (38.2)	19.80 (36.2)
36	9.41 (53.1)	8.28 (51.0)
48	3.76 (87.6)	3.02 (93.4)

			90% CI
AUC(0-t) (ng.hr/mL)	1132.0 (25.9)	1075.0 (27.0)	
AUCINf (ng.hr/mL)	1213.0 (25.7)	1146.0 (26.7)	
Cpeak(ng/mL)	68.9 (34.3)	66.7 (37.6)	
Tpeak (hr)	7.66	6.77	
Kel(1/hr)	0.072	0.073	
T1/2(hr)	10.1	9.77	
LnAUC(0-t)			89-100%
LnAUCI			89-99%
LnCpeak			88-105%

1. For norverapamil, the means for AUC(0-t), AUCI and Cpeak values were 5.0%, 5.5% and 3.2% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The norverapamil plasma levels peaked at 6 hours for both the test and the reference products following their administration under fasting conditions.

V. Formulation:

Mylan's formulations for its verapamil HCl ER 180 and 240 mg tablet are shown below:

Verapamil HCl Extended-Release Tablets 180 and 240 mg

	MG Per Tablet	
Active Component		
Verapamil HCl, USP	180.0	240.0
Inactive Components		
Povidone, USP		

Purified Water, USP		
Sodium Alginate NF		
Microcrystalline Cellulose NF		
Magnesium Stearate/ Sodium Lauryl Sulfate		
Total	525.0	700.0
Inactive Components (Film-Coat)		
(Blue		
Total contribution from Blue coating suspension	16.0	17.95

* Solids consist of polydextrose, hydroxypropyl methylcellulose, titanium dioxide, triacetin, polyethylene glycol, and FD&C Blue #1 Aluminum Lake.

[1] Purified Water, USP is added to the product as a processing aid but does not contribute to the total weight, therefore, Purified Water, USP quantities are expressed parenthetically.

VI. In vitro Dissolution Testing:

Method: USP 23 apparatus II (paddle) at 50 rpm
Medium: 900 mL of Simulated Gastric Fluid T.S (no enzyme) for one hour, then Simulated Intestinal Fluid T.S. (no enzyme) for 2, 3.5, 5 and 8 hours.
Number of Tablets: 12
Test Product: Mylan's Verapamil HCl ER tablets, 180 mg Lot #2B005H
Reference Product: Knoll's Isoptin® SR tablet, 180 mg lot #21290016.

The dissolution testing results are presented in table III.

The dissolution specifications for the 180 mg strength are the same as the previcusly approved 240 mg strength.

VII. Comments:

1. The firm's single-dose bioequivalence study #ISOP-9662 under

fasting conditions, conducted on its 180 mg verapamil HCl ER tablet is acceptable. The two study drugs did not differ significantly with respect to mean values for any of the pharmacokinetics parameters. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCpeak are within the acceptable range of 80-125% for verapamil and norverapamil

2. The in vitro dissolution testing for the test product 180 mg verapamil HCl ER tablets is acceptable.

3. The firm currently holds an approved ANDA #74-587 for Verapamil HCl Extended-release Tablets 240 mg since March 23, 1996.

4. It should be noted that the formulation for the 180 mg strength is qualitatively the same as for the 240 mg strength and there are slight quantitative differences.

VIII. Recommendations:

1. The single-dose bioequivalence study #ISOP-9662, conducted by Mylan Pharmaceuticals Inc., on its verapamil HCl 180 mg extended release (ER) tablet, lot #2B005H, comparing it to Isoptin^{R} SR 180 mg tablet manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's verapamil HCl ER tablet 180 mg is bioequivalent to Knoll's Isoptin® SR tablet 180 mg.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc., on its verapamil HCl 180 mg ER tablets, lot #2B005H is acceptable. The dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme (first hour) and 900 mL of simulated intestinal fluid without enzyme (second hour and thereafter) at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The following specifications are recommended:

1
2
3.5
5
8

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Date: 7/14/97

Concur: _____ Date: 9/15/97

Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

Mmakary/7-11-97 wp 74587SD.297
cc: ANDA #74-587, original, HFD-650 (Director), HFD-658 (Makary), Drug File, Division File.

Table III In Vitro Dissolution Testing

Drug (Generic Name):Verapamil ER
Dose Strength:180 mg Tablets
ANDA No.:74-275
Firm: Mylan Pharmaceuticals Inc.
Submission Date: February 18, 1997
File Name: 74587SD.297

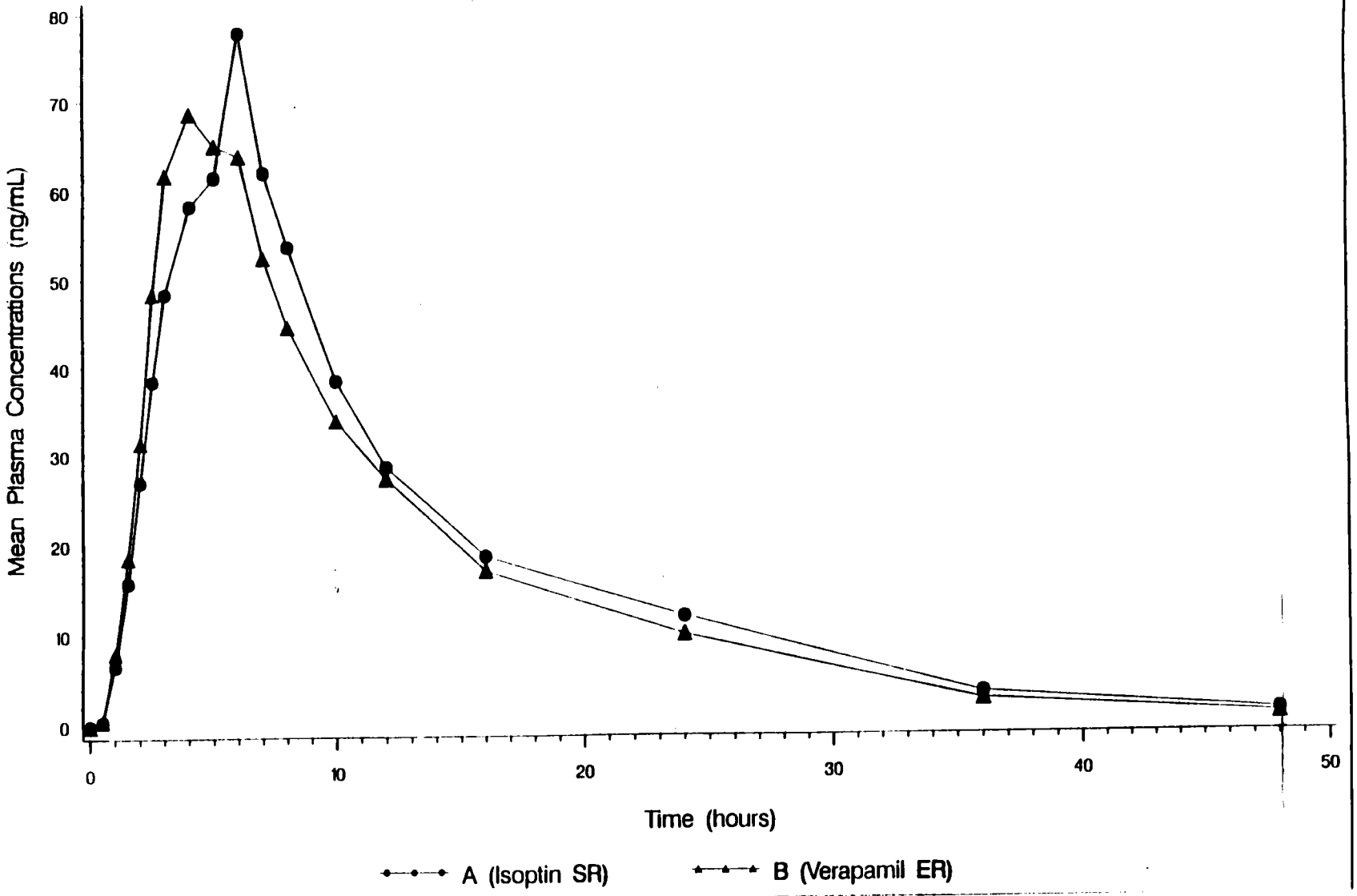
I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium:900 mL SGF for 1 hour, then SIF
Specifications:
Reference Drug: Knoll's Isoptin SR tablets, 180 mg
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot #2B005H Strength(mg) 180			Reference Product Lot #21290016 Strength(mg) 180		
	Mean %	Range	%CV	Mean %	Range	%CV
1	18		2.1	14		6.1
2	28		2.6	22		6.5
3.5	50		4.2	43		5.5
5	70		5.8	65		5.7
8	96		5.1	96		3.8

Mean Verapamil Plasma Concentrations
N= 47

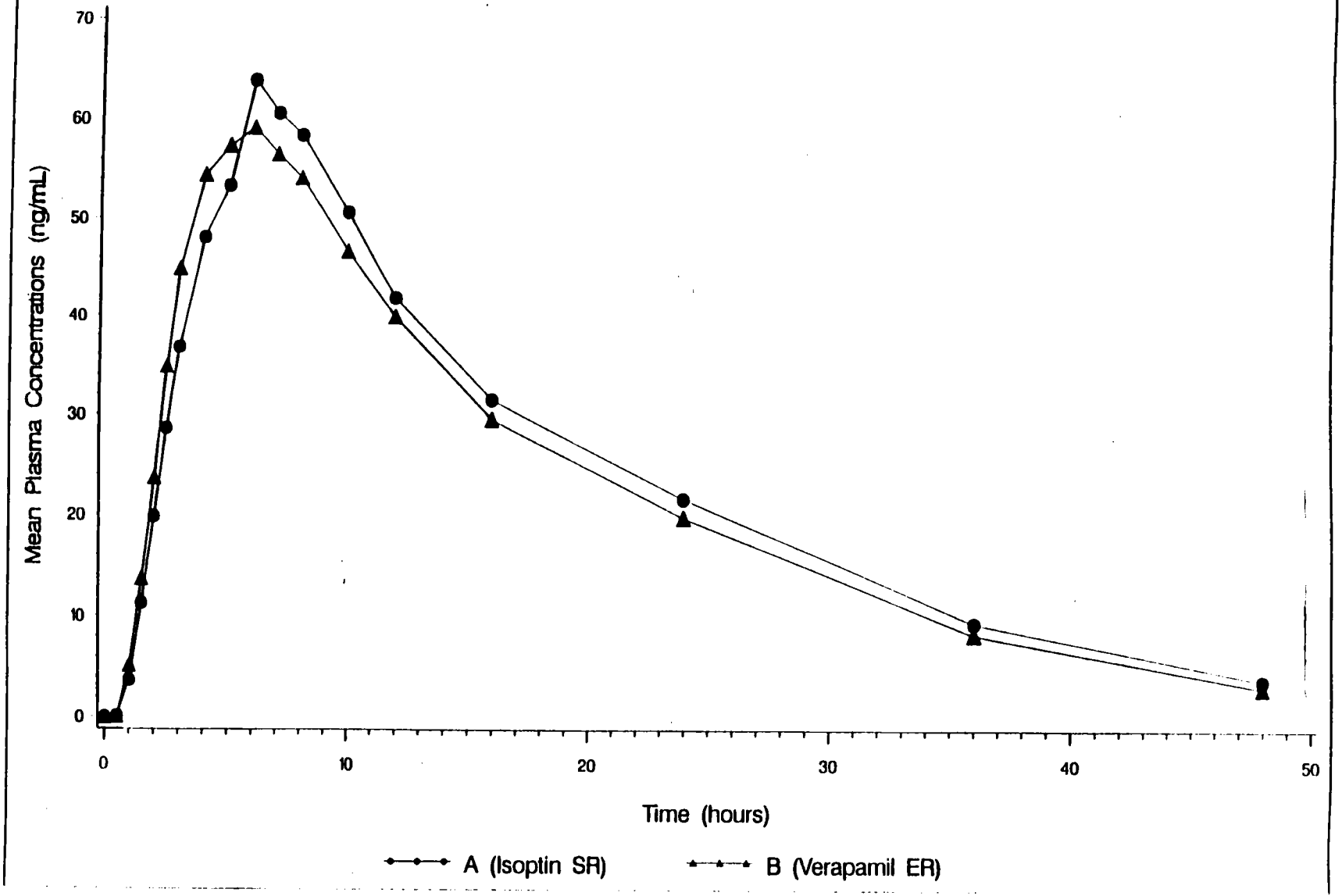


VERAPAMIL ER (ISOP.–9662)

Total Dose: 180 mg (1x180mg Tablet), Study Type: Fasting

Mean Norverapamil Plasma Concentrations

N= 47



DIV

ANDA 74-587

FEB 12 1996

Mylan Pharmaceuticals Inc.
Attention: W. Bradley McMillen
781 Chestnut Ridge Road
P.O. BOX 4310
Morgantown WV 26504-4310

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Verapamil Hydrochloride Extended-release Tablets 240 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme (first hour) and 900 mL of simulated intestinal fluid without enzyme (second hour and thereafter) at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The following tentative specifications are recommended:

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

FEB 2 1996

Verapamil HCl ER Tablets
240 mg
ANDA #74-587
Reviewer: Moheb H. Makary
WP 74587SDW.995

Mylan Pharmaceutical Inc.
Morgantown, WV
Submission Date:
September 22, 1995

Review of An Amendment to bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective:

The firm has replied to the reviewer's comment made in the review of the December 12, 1994 submission (three bioequivalence studies , dissolution data and waiver request). The firm was asked to submit a comparative dissolution testing on half-tablets [test (coated and uncoated) versus reference product].

II. Comments:

1. The firm submitted half-tablet dissolution testing on its Verapamil HCl ER Tablet, 240 mg, Mylan's lot#2Z004K and Isoptin^R lot #21300333 (biobatches). For Mylan's product, both uncoated (core) and coated tablet were tested. The dissolution testing results are shown in Table I.

2. The dissolution results indicate that, in general, a higher dissolution was observed for the half-tablets at each sampling time compared to the whole tablets of the test product. However, the magnitude of the increase is similar when comparing Mylan's product to the innovator product. The dissolution testing is acceptable.

3. The firm proposed dissolution specifications that they would like to use which are as follows:

1 hour
2 hours
3.5 hours
5 hours
8 hours

The dissolution specifications are acknowledged.

These specifications are almost the same as the recommended specifications in the review of 8/4/95 (ANDA #74-587, submission dated December 12, 1994).

III. Recommendations:

1. The single-dose bioequivalence study #9321, conducted by Mylan Pharmaceuticals Inc., on its verapamil HCl 240 mg extended release (ER) tablets, lot #2Z004K, comparing it to

Isoptin^R SR 240 mg tablets manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's verapamil HCl ER tablets 240 mg is bioequivalent to Knoll's Isoptin® SR tablets 240 mg.

2. The single-dose post-prandial bioequivalence study #9322, conducted by Mylan Pharmaceuticals Inc., on its verapamil HCl 240 mg ER tablets, lot #2Z004K, comparing it to Isoptin^R SR 240 mg tablets manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's verapamil HCl ER tablets 240 mg is bioequivalent to Knoll's Isoptin® SR tablets 240 mg.

3. The multiple-dose steady-state bioequivalence study #9418, conducted by Mylan Pharmaceuticals Inc., on its verapamil HCl 240 mg ER tablets, lot #2Z004K, comparing it to Isoptin^R SR 240 mg tablets manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's verapamil HCl ER tablets 240 mg is bioequivalent to Knoll's Isoptin® SR tablets 240 mg.

4. The dissolution testing conducting by Mylan Pharmaceuticals Inc., on its verapamil HCl 240 mg ER coated tablets (whole and half-tablets), lot #2Z004K is acceptable. The dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme (first hour) and 900 mL of simulated intestinal fluid without enzyme (second hour and thereafter) at 37^{0}C using USP 23 apparatus II (paddle) at 50 rpm. The following tentative specifications are recommended:

1
2
3.5
5
8

5. Waiver of the in vivo bioequivalence study requirements for the firm's Verapamil HCl Extended Release tablets, 240 mg, is granted.

6. From the bioequivalence point of view the firm has met the requirements of in vivo bioequivalence and in vitro dissolution testing and the application is approvable.

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Date: 1/31/96

Concur: _____ Date: 2/2/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/1-31-96 wp 74587SDW.994
cc: ANDA #74-587, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Table I In Vitro Dissolution Testing

Drug (Generic Name):Verapamil ER
Dose Strength:240 mg Tablets
ANDA No.:74-275
Firm: Mylan Pharmaceuticals Inc.
Submission Date: September 22, 1995
File Name: 74587SDW.D94

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium:900 mL SGF for 1 hour, then SIF
Specifications:
Reference Drug: Knoll's Isoptin SR tablets, 240 mg
Assay Methodology

II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product 1/2 Tablet Lot #2Z004K (Core) Strength(mg) 240			Reference Product 1/2 Tab Lot # 21300333 Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
1	19		7.3	19		7.3
2	29		9.3	30		9.2
3.5	47		10.1	49		9.1
5	65		7.9	68		7.0
8	94		5.8	100		4.4

Sampling Times (Minutes)	Test Product 1/2 Tablet Lot # 2Z004K Coated Strength(mg) 240			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
1	18		5.5			
2	28		7.5			
3.5	47		7.6			
5	68		7.4			
8	100		4.0			

Sampling Times (Minutes)	Test Product Whole Tablet Lot # 2Z004K Strength(mg) 240			Reference Product Whole Lot # 31200333 Tablet Strength(mg) 240		
	Mean %	Range	%CV	Mean %	Range	%CV
1	12.0		8.2	13.3		15.6
2	19.2		9.0	22.4		16.4
3.5	33.0		5.9	37.5		9.8
5	50.3		9.3	57.5		7.7
8	92.4		3.8	91.2		5.2

OCT 7 1996

Verapamil HCl ER Tablet
120 mg
ANDA #74-587
Reviewer: Moheb H. Makary
WP 74587SD.496

Mylan Pharmaceuticals Inc
Morgantown, West Virginia
Submission ~~Date:~~
April 4, 1996

Review of Bioequivalence Studies and Dissolution Data

I. Objective:

The firm submitted three bioequivalence studies to assess the bioequivalence of the Mylan's Verapamil HCl Extended-release Tablets, 120 mg, to Knoll's Isoptin^{R} SR 120 mg Tablets. Dissolution profiles comparing Mylan's Verapamil HCl Extended-release 120 mg tablets to Isoptin® tablets were submitted. Comparative composition was also submitted.
The firm currently holds an approved ANDA #74-587 for Verapamil HCl Extended-release Tablets 240 mg since March 23, 1996.
It should be noted that the formulation for the 120 mg strength is qualitatively the same as for the 240 mg strength and there are slight quantitative differences.

The following studies were performed and included in the submission:

1. Study #Vera-9523a
A two-way crossover, single-dose bioequivalence study of verapamil HCl 120 mg Extended-release (ER) tablets under fasting conditions.

2. Study #Vera-9578
A three-way crossover, single-dose, post-prandial bioequivalence study of verapamil HCl 120 mg ER tablets.

3. Study #Vera-9579
A two-way crossover, multiple-dose bioequivalence study of verapamil HCl 120 mg ER tablets.

II. Background:

Verapamil is a calcium-channel blocking agent. Its mechanism of action involves inhibition of ATP-dependent calcium transport properties of the sarcolemma and intrinsic calcium-sensitive ATPase. The drug is well absorbed orally (over 90%). However, extensive first-pass metabolism reduces absolute bioavailability to approximately 20%. An N-dealkylated metabolite, norverapamil, is active and upon single dose administration the AUC of this

metabolite equals or exceeds that of the parent drug. The mean elimination half-life for verapamil in single dose studies ranged from 2.8 to 7.4 hours.
As an anti-anginal agent, the usual dose is 80-120 mg three times daily. As an anti-arrhythmic, the usual dose ranges from 240-320 mg or from 240-480 mg per day (in 3 or 4 divided doses). To treat essential hypertension, the usual initial dose for monotherapy is 80 mg three times daily, individualized to 360 mg daily.
Verapamil HCl is marketed as 80 and 120 mg conventional release tablets. The drug is also marketed as a 120 mg, 180 mg and 240 mg sustained release tablets for treatment of essential hypertension. The usual daily dose is 240 mg once daily in the morning. Labeling describes higher doses if necessary. Labeling also indicates that the drug should be dosed with food.

III. Study #Vera-9523a For Single-Dose, Two-Way Crossover Of Verapamil HCl Extended-release Tablets, 120 mg, Under Fasting Conditions:

The objective of the study was to compare the bioavailability of verapamil-ER 120 mg tablets manufactured by Mylan Pharmaceuticals Inc., with that of Knoll product (Isoptin^{R} SR), following an oral administration of a single 240 mg dose (2x120 mg tablets) of each product under fasting conditions.

Clinical site:

Analytical site:

Investigators:

Study design: Single-dose, two-way crossover bioequivalence study, under fasting conditions.

Subjects: Thirty-eight (38) male subjects were accepted for entry into the clinical portion of the study. Thirty-eight (38) subjects successfully completed both phases of the clinical portion of the study. The clinic portion of the study was conducted in two groups for safety to insure prompt evaluations of the ECG PR intervals. Group A consisted of volunteer 1-14 and Group B was volunteers 15-38. The dosing dates for this study were as following:

	Phase I	Phase II
Group A	August 26	September 7, 1995

Group B September 16 September 28, 1995

Selection criteria: The subjects were between 19 to 45 years of age. All subjects were within ±10% of their ideal body weight for height and body frame as described in the Metropolitan Life Insurance Company Statistical Bulletin, 1983. Subjects were judged to be in good health following a complete physical examination, EKG and medical history within fourteen days of the start of the study. In addition, urine samples at the time of the medical examination were free of drug abuse (including marijuana). Good health was confirmed by normal findings in the following tests: biochemical profile, hematology and urinalysis.

Exclusion criteria: Consisted of adverse reactions or allergy to verapamil or any other calcium channel blockers, history of alcohol or drug abuse, history of cardiovascular, neurological, neuropsychiatric, gastrointestinal, hepatic, renal, hematological and/or respiratory diseases.

Restrictions: Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. In addition, no concomitant medication is permitted during the study period. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine-containing products for 48 hours prior to, and during the course of the study.

Dose and treatment: Treatment A: 2x120 mg verapamil HCl ER tablet (Mylan), lot #2B006H, batch size Tablets, potency 95.4%, content uniformity 97.3% (CV=1.2%), administered following a 10 hours overnight fast.

Treatment B: 2x120 mg Isoptin®SR tablet (Knoll), lot #20900074, Exp. 4/97, potency 98.8%, content uniformity 99.3% (CV=1.4%), administered following a 10 hours overnight fast.

Washout period: A twelve day washout period separated each phase.

Food and fluid

intake:	Subjects fasted for ten hours prior to dosing. Lunch was served five hours after dosing. Dinner was served ten hours after dosing. Water was not allowed two hours before until two hours after dosing, except for the dosing water (240 mL).
Blood samples:	Ten mL (10) blood samples were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, and 48 hours after dosing. Plasma samples were immediately frozen.
Subject welfare:	Vital signs (blood pressure, pulse rate and Lead II ECG) were measured pre-dose and hourly for eight hours after dosing and at 12, 24 and 48 hours.

Assay Methodology:

Statistical Analysis:

Statistical analysis was performed on verapamil and norverapamil data using SAS. Analysis of variance was performed using the GLM procedure. Pharmacokinetic parameters were evaluated for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval. The subjects in the study were dosed in two separate groups. Group A consisted of subjects numbered 1 to 14 and group B consisted subjects numbered 15 to 38. An analysis of variance was performed to assess the group effect and determine the poolability of the two groups.. A mode with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, treatments and periods was performed. No statistically significant group effects were observed for the pharmacokinetic parameters by using the above model. The firm dropped the group effect, and the standard two way crossover model was employed.

IV. In Vivo Results:

Thirty-nine (38) normal, healthy subjects were recruited for the

study and successfully completed both phases of the clinical portion of the study. The clinic was conducted in two groups for safety to insure prompt evaluations of the EKG PR intervals. Group A consisted of subjects numbered 1 to 14 and group B consisted subjects numbered 15 to 38.
Ten adverse events (headache, lightheadedness or nausea) were reported in eight subjects dosed over the course of the study. Of the ten reported adverse events, nine were probably or possibly related to the study drug.

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables I and II.

Table I

Mean Plasma Verapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Verapamil HCl ER (2x120 mg Tablets) under Fasting Conditions
(N=38)

Time hr	Treatment A Mylan-Test Lot #2B006H ng/mL(CV)	Treatment B Reference Lot #20900074 ng/mL(CV)
0	0	0
0.5	1.61 (194)	1.30 (206)
1	11.72 (72.3)	12.88 (133)
1.5	25.94 (60.2)	31.54 (112)
2	44.28 (62.1)	54.61 (96.1)
2.5	62.09 (67.1)	69.40 (79.0)
3	75.55 (64.1)	83.11 (72.4)
4	89.82 (67.0)	91.40 (62.9)
5	88.20 (62.1)	92.61 (53.1)
6	93.90 (40.1)	104.73 (48.8)
7	75.66 (37.4)	82.92 (46.7)
8	65.41 (37.4)	70.58 (45.8)
10	49.86 (36.9)	50.75 (41.1)
12	39.75 (45.7)	40.30 (45.5)
16	25.28 (50.9)	25.31 (47.3)
24	15.79 (67.1)	15.15 (24.7)
36	4.44 (90.6)	4.75 (74.2)
48	1.28 (159)	1.06 (170)

			90% CI
AUC(0-t) (ng.hr/mL)	1141.48 (37.6)	1189.52 (43.0)	
AUCINf (ng.hr/mL)	1200.40 (35.7)	1249.12 (40.9)	

Cpeak(ng/mL)	115.12 (46.1)	117.92 (46.6)	
Tpeak (hr)	5.43	5.57	
Kel(1/hr)	0.086	0.086	
T1/2(hr)	8.33	8.44	
LnAUC(0-t)			89-107%
LnAUCI			90-107%
LnCpeak			88-113%

Table II

Mean Plasma Norverapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 Verapamil HCl ER (2x120 mg Tablets) under Fasting Conditions
(N=38)

Time hr	Treatment A Mylan-Test Lot #2B006H ng/mL(CV)	Treatment B Reference Lot #20900074 ng/mL(CV)
0	0	0
0.5	0.46 (356)	0.34 (295)
1	7.42 (74.3)	7.21 (111)
1.5	19.13 (55.0)	18.76 (83.1)
2	31.92 (49.0)	33.78 (69.3)
2.5	44.78 (51.1)	45.89 (54.3)
3	55.46 (45.3)	57.89 (48.7)
4	68.88 (44.3)	70.55 (45.5)
5	74.25 (41.3)	77.76 (39.6)
6	81.59 (33.9)	87.38 (35.9)
7	77.08 (31.5)	82.38 (33.3)
8	74.79 (29.5)	79.66 (32.7)
10	66.28 (26.6)	68.05 (26.8)
12	56.31 (25.4)	58.32 (23.7)
16	41.39 (27.8)	42.00 (24.6)
24	28.83 (34.8)	28.54 (30.1)
36	11.89 (46.7)	11.81 (43.9)
48	4.86 (73.9)	4.58 (66.6)

			90% CI
AUC(0-t) (ng.hr/mL)	1508.90 (24.6)	1538.84 (24.4)	
AUCINf (ng.hr/mL)	1598.80 (24.4)	1626.37 (23.9)	
Cpeak(ng/mL)	87.31 (28.9)	91.49 (31.8)	
Tpeak (hr)	6.53	6.66	
Kel(1/hr)	0.073	0.08	
T1/2(hr)	9.71	9.42	

LnAUC(0-t)	93-104%
LnAUCI	93-104%
LnCpeak	89-104%

1. For verapamil, the least squares means for AUC(0-t), AUCI and Cpeak values were 4.0%, 3.9% and 2.4% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

2. The verapamil and norverapamil plasma levels peaked at 6 hours for both the test and the reference products following their administration under fasting conditions.

3. For norverapamil, the least squares means for AUC(0-t), AUCI and Cpeak values were 1.9%, 1.7% and 4.6% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for the log-transformed data. The reviewer's calculations are similar to those submitted by the firm.

4. Analysis of variance (ANOVA) of verapamil and norverapamil showed no statistically significant sequence, period or treatment effect for AUC(0-t), AUCI and Cpeak.

5. Systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval were analyzed for statistical differences. There were no clinically significant differences in the parameters evaluated.

V. Study #Vera-9578 For Post-Prandial Single-Dose Bioequivalence Study

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of Mylan's verapamil HCl 120 mg ER tablets relative to Isoptin^R SR 120 mg Tablets (Knoll), following administration of a 240 mg dose (2 tablets).

Clinical site:

Analytical site:

Study date: Clinical phase: November 18, - December 18, 1995
Analytical phase: December 21, 1995 - January 27, 1996

Investigators:

Study design:	Single-dose, three-way crossover, post-prandial bioequivalence study.
Subjects:	The study was conducted in eighteen (18) normal, healthy non-smoking, male subjects. They were accepted into the study following informed consent, physical examination and blood and urine analysis. All subjects successfully completed all three phases of the study. These subjects ranged in age from 18 to 45 years.
Selection criteria, Exclusion criteria, & Restrictions:	Please see Study #Vera-9523a for single-dose under fasting conditions above.
Washout period:	Two weeks
Dose and treatment:	Treatment A: 2x120 mg verapamil HCl ER tablets (Mylan Pharmaceuticals Inc), lot #2B006H administered following an overnight fast. Treatment B: 2x120 mg verapamil HCl ER tablets (Mylan Pharmaceuticals Inc), lot #2B006H administered within 30 minutes of a high fat breakfast preceded by an overnight fast. Treatment C: 2x120 mg Isoptin® SR tablets (Knoll), lot #20900074, administered within 30 minutes of a high fat breakfast preceded by an overnight fast.
Food and fluid intake:	Subjects were required to fast overnight for 10 hours prior to dosing in each treatment phase. Subjects on regimen A ingested the two tablets with 240 mL of water. Subjects on regimen B and C ingested the two tablets with 240 mL of water within 30 minutes after a standardized high-fat breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk

and 6 ounces of orange juice). Lunch and dinner were served at 5 and 10 hours, respectively, post-dose. Water was not permitted two hours before and two hours after dosing, but was allowed at all other times.

Blood samples: Ten (10) mL of blood were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36 and 48 hours after drug administration. Blood collections were centrifuged at $4^{0}C$ and plasma samples were immediately frozen.

Assay Methodology: Please see study #Vera-9523a above.

Statistical Analysis

Cpeak for verapamil and norverapamil was determined by establishing the peak concentration for each subject. The areas under the plasma verapamil and norverapamil concentration versus time curves (AUCs) were calculated by using the linear trapezoidal rule.

VI. In Vivo Results:

This study was conducted from November 18, 1995 to December 18, 1995 in the

Eighteen healthy male volunteers were accepted for entry into the clinical phase of the study. Eighteen subjects successfully completed all three phases of the clinical portion of the study. There were fourteen medical events reported for this study. Three of which were reported prior to dosing. Of the eleven reported during the study, four were probably drug related. These were three reports of a headache and one report of feeling lethargic.

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables III and IV.

Table III

Mean Plasma Verapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 mg Verapamil HCl ER (2x120 mg Tablets) Under Fasting and Nonfasting Conditions

(N=18)

Time hr	Treatment A Mylan Lot #2B006H Fasting ng/mL (CV)	Treatment B Mylan Lot #2B006H Nonfasting ng/mL (CV)	Treatment C Isoptin® Lot #20900074 Nonfasting ng/mL (CV)	
0	0	0	0	
0.5	1.20 (285.3)	0.51 (232.6)	0	
1	14.88 (115.1)	5.93 (113.0)	1.68 (172.6)	
1.5	33.91 (92.3)	13.59 (106.3)	6.40 (131.5)	
2	60.44 (77.1)	21.01 (124.2)	11.29 (106.8)	
2.5	90.61 (72.7)	29.44 (122.7)	15.21 (85.9)	
3	111.73 (70.8)	34.47 (110.4)	18.91 (79.6)	
4	142.52 (73.3)	46.90 (79.8)	32.97 (73.8)	
5	139.24 (78.1)	62.50 (83.1)	63.16 (127.1)	
6	142.49 (62.3)	98.89 (79.1)	113.26 (114.9)	
7	120.58 (55.1)	114.89 (73.8)	105.07 (93.3)	
8	101.61 (51.7)	115.14 (67.8)	103.30 (95.2)	
10	72.80 (54.1)	95.45 (73.2)	83.84 (74.1)	
12	56.52 (72.8)	67.77 (61.0)	62.98 (68.7)	
16	36.11 (111.5)	37.31 (67.7)	35.90 (151.1)	
24	21.40 (134.1)	21.69 (83.0)	21.08 (74.2)	
36	5.65 (201.9)	6.24 (129.7)	5.52 (131.5)	
48	2.54 (234.5)	2.03 (206.8)	1.89 (182.7)	
				B/C
AUC(0-t) (ng.hr/mL)	1677.7 (70.8)	1461.4 (72.4)	1337.0 (83.7)	1.09
AUCinf (ng.hr/mL)	1769.9 (69.8)	1516.3 (72.8)	1398.5 (81.9)	1.08
Cpeak(ng/mL)	178.5 (55.9)	130.3 (70.1)	125.1 (103)	1.04
Tpeak (hr)	5.39	7.67	7.22	
T1/2 (hr)	8.19	7.18	7.48	
Kel(hr^{-1})	0.0893	0.1003	0.0980	

Table IV

Mean Plasma Norverapamil Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 240 mg Verapamil HCl ER (2x120 mg Tablets) Under Fasting and Nonfasting Conditions
(N=18)

Time hr	Treatment A Mylan Lot #2B006H Fasting ng/mL (CV)	Treatment B Mylan Lot #2B006H Nonfasting ng/mL (CV)	Treatment C Isoptin® Lot #20900074 Nonfasting ng/mL (CV)	
0	0	0	0	
0.5	0.42 (292.0)	0	0	
1	7.29 (83.1)	1.94 (157.7)	0.40 (291.6)	
1.5	20.09 (72.0)	6.86 (91.6)	2.83 (149.2)	
2	35.93 (62.3)	11.95 (94.6)	6.88 (92.9)	
2.5	56.37 (55.5)	19.15 (93.8)	11.26 (70.9)	
3	71.40 (53.6)	24.57 (85.6)	14.73 (59.0)	
4	97.73 (73.3)	39.01 (57.9)	27.37 (42.8)	
5	108.66 (56.6)	54.31 (37.9)	45.02 (36.8)	
6	120.15 (47.3)	79.39 (26.6)	77.86 (34.3)	
7	117.79 (41.9)	94.76 (29.3)	87.95 (30.6)	
8	114.46 (38.5)	104.94 (35.8)	96.87 (33.2)	
10	99.28 (33.9)	107.62 (39.6)	98.89 (37.7)	
12	80.62 (32.1)	94.08 (35.6)	88.50 (36.8)	
16	56.76 (33.1)	65.76 (34.9)	63.98 (33.7)	
24	35.87 (43.5)	41.85 (44.3)	41.97 (42.1)	
36	13.94 (76.2)	15.79 (66.9)	15.57 (64.2)	
48	6.94 (105.2)	8.09 (82.8)	7.83 (75.4)	
				B/C
AUC(0-t) (ng.hr/mL)	2072.6 (32.2)	2010.9 (34.4)	1905.9 (35.9)	1.06
AUCinf (ng.hr/mL)	2209.3 (34.4)	2143.7 (37.6)	2027.3 (39.2)	1.06
Cpeak(ng/mL)	132.4 (38.5)	114.7 (35.8)	103.3 (35.4)	1.11
Tpeak (hr)	6.83	8.94	9.33	
T1/2 (hr)	9.89	9.60	9.53	
Kel(hr^{-1})	0.0739	0.0749	0.0746	

Verapamil

1. The verapamil plasma levels peaked at 6 and 8 hours for the reference and test products, respectively, under nonfasting conditions and at 4 hours for the test product under fasting conditions.

2. For Mylan's test product, the mean AUC(0-t), AUCinf and Cpeak values were 9.3%, 8.4%, 4.2%, higher, respectively, than the reference product values under nonfasting conditions. The ratios

of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax.

3. For the test product, the mean Cpeak value after dosing with food was about 73.0% of the value reported in the fasting state. Also, after feeding the Tpeak was delayed about 2.3 hours relative to the fasting Tpeak.

4. There were no statistically significant carry-over effects for AUC(0-t), AUCinf and Cpeak between the three treatments.

Norverapamil

1. The norverapamil plasma levels peaked at 10 hours for both test and reference products under nonfasting conditions and at 6 hours for the test product under fasting conditions.

2. For Mylan's test product, the mean AUC(0-t), AUCinf and Cpeak values were 5.5%, 5.7% and 11.0% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cpeak.

3. For the test product, the mean Cpeak value after dosing with food was about 86.6% of the value reported in the fasting state. Also, after feeding the Tpeak was delayed about 2.1 hours relative to the fasting Tpeak.

4. There were no statistically significant carry-over effects for AUC(0-t), AUCinf and Cpeak between the three treatments.

VII. Study #Vera-9579, Multiple-dose Bioequivalence study of Verapamil HCl 120 mg ER Tablets

The objective of the study was to assess the bioavailablity at steady-state of verapamil HCl 120 mg ER tablets (Mylan) as compared to Isoptin^{R} SR 120 mg Tablets (Knoll) following once-a-day dosing of each formulation for eight days.

Clinical site:

Analytical site:

Study date: Clinical phase: December 11,1995 - February 2, 1996
Analytical phase: February 1, 1996 -February 27, 1996

Investigators:

Study design: Two-way crossover, multiple-dose study

Subjects: Forty healthy male subjects were accepted for entry into the clinical phase of the study and dosed. Due to dropouts (adverse events (11 subjects), possible food poisoning (10 subjects) and one dropout for personal reasons) an additional group (Group 2) of twelve subjects was recruited into the study (three of the subjects in Group 2 dropped from the study for personal reasons). Twenty-seven (27) subjects successfully completed both phases of the clinical portion of the study. The dosing dates for this study presented as following:

	Phase I	Phase II
Group 1	December 11, 1995	January 4, 1996
Group 2	January 4, 1996	January 25, 1996

Group 1 Subjects #1-40
Group 2 Subjects #104, 105, 106, 107, 110, 111, 113, 114, 119, 120, 122 and 124.

Washout period: The washout period for Group 1 was seventeen days and for Group 2 was fourteen days.

Selection criteria, Exclusion criteria, and Restrictions: Please see study #Vera-9523a for the single dose .

Vital signs: Vital signs (including blood pressure, pulse rates) were measured before each dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours following the first and eighth drug administration. Lead II EKGs were performed for safety after the first seven doses at 4, 6 and 8 hours post dose. Lead II EKGs were also performed for each subject one hour before the eighth dose and at 1, 2, 3, 4, 5, 6,7,8, 10, 12, 16 and 24 hours after the eighth dose. If a subject's PR interval was greater than 0.28 seconds on any of the EKGs, the subject withdrew from the study and

repeat EKGs were taken until the PR interval returned to <0.22 seconds. If a subject's PR interval was ≥ 0.24 seconds before any of the remaining doses, the subject was not dosed and withdrew from the study. If the PR interval was ≥ 0.22 and ≤ 0.28 after dosing, repeat EKGs were performed. The subject received the next dose if the PR interval returned to <0.24 seconds.

Dose and treatment: Treatment A
Day 1-7: 2x120 mg Verapamil® HCl ER Tablets (Mylan Pharmaceuticals Inc), lot #2B006H administered with 240 mL of water at 8 AM.
Day 8: 2x120 mg Verapamil HCl ER Tablets (Mylan Pharmaceuticals Inc), lot #2B006H administered with 240 mL of water at 8 AM following a 10 hour overnight fast.
Treatment B
Days 1-7: 2x120 mg Isoptin® SR Tablets (Knoll), lot #20900074 administered with 240 mL of water at 8 AM.
Day 8: 2x120 mg Isoptin® SR Tablets (Knoll), lot #20900074 administered with 240 mL of water at 8 AM following a 10 hour overnight fast.

Food and fluid intake: Subjects fasted for ten hours prior to dosing. Lunch was served five hours after dosing. Dinner was served ten hours after dosing. Water was not allowed two hours before until two hours after dosing, except for the dosing water (240 mL).

Blood samples: Blood samples were collected during each study period at:
Day 1: 0 hour (pre-drug)
Day 6: 0 hour (pre-drug)
Day 7: 0 hour (pre-drug)
Day 8: 0 hour (pre-drug), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 16 and 24 hours following drug administration. Plasma samples were separated and stored at -20°C.

Assay Methodology: Please see study #Vera-9523a for the single dose.

Statistical Analysis:

Statistical analysis was performed using SAS-GLM. ANOVA was performed using GLM. Pharmacokinetic parameters were evaluated

for treatment, sequence and period effects. The two one-sided tests were used to estimate the 90% confidence interval for the pharmacokinetic parameters. An analysis of variance was performed to assess the group effect. A model with terms for groups, sequences, group by sequence interaction, subjects within the group by sequence interaction, treatments and periods was performed. An analysis of steady-state attainment was performed using Cmin data from the 120, 144 and 168 hours plasma samples.

VIII. In Vivo Results

Initially, forty (40) subjects enrolled in this study. Of these forty subjects, twenty-two did not complete the crossover. Ten subjects were withdrawn due to known cardiac effects of the drug as determined by EKG (asymptomatic) and one volunteer chose to withdraw due nausea. There were also 10 subjects withdrawn from the study that experienced medical events not related to the study medication (loose stools), possible food poisoning. In order to replace subjects who had been discontinued from the study, twelve (12) additional healthy male volunteers enrolled in the study (as a Group 2). Of these twelve subjects, three subjects dropped from the study for personal reasons and did not complete the crossover. Twenty-seven (27) subjects successfully completed both phases of the clinical portion of the study. There were 256 medical events reported for this study during the eight days of dosing. Of these 108 were assessed as drug related medical events. The results indicate that the incidence of adverse experiences were similar between the test and reference products. There were no serious or life-threatening medical events reported in the study.

The plasma concentrations and pharmacokinetic parameters for verapamil and norverapamil are summarized in Tables V and VI.

Table V

Mean Verapamil Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (8x240 mg) of Verapamil HCl ER 120 mg Tablets
(N=27)

Time hr	Treatment A Mylan Lot #2B006H ng/mL (CV)	Treatment B Isoptin® Lot #20900074 ng/mL (CV)
0	0.00	0.00
120	40.66 (56.0)	36.30 (59.2)
144	34.43 (48.8)	35.34 (59.6)
168	36.17 (52.0)	35.04 (55.1)

168.5	37.84 (52.8)	34.84 (56.6)
169	57.92 (47.8)	52.88 (56.2)
169.5	80.92 (40.2)	80.18 (56.8)
170	109.11 (37.8)	112.41 (62.1)
170.5	141.03 (39.3)	138.00 (88.8)
171	165.87 (38.3)	171.82 (53.8)
172	195.05 (32.6)	204.21 (45.5)
173	205.71 (33.2)	219.16 (42.4)
174	208.12 (31.9)	221.31 (37.8)
175	191.69 (32.4)	193.63 (34.7)
176	164.85 (32.0)	168.30 (38.2)
178	128.99 (36.9)	128.97 (34.2)
180	96.23 (41.4)	96.99 (41.1)
184	57.64 (55.8)	56.30 (52.4)
192	37.71 (69.1)	34.66 (59.1)

			90% CI
AUC(0-24)(ng.hr/mL)	2438.1 (33.5)	2467.1 (37.0)	
Cpeak (ng/mL)	227.3 (28.7)	240.0 (37.4)	
Cmin (ng/mL)	33.9 (56.2)	30.7 (54.3)	
Tpeak (hr)	173.3	173.3	
Css (ng/mL)	101.6 (33.5)	102.8 (37.2)	
Fluct1 (%)	198.3 (27.6)	208.6 (26.3)	
Fluct2 (%)	717.2 (50.3)	846.0 (50.0)	
LnAUC(0-24)			94-106%
LnCpeak			89-104%

*Fluct1 = (Cpeak-Cmin)/Css*100
**Fluct2 = (Cpeak-Cmin)/Cmin*100
Cmin = Min. Conc. from time range 168-192 hours
Css = AUC/24

Table VI

Mean Norverapamil Plasma Concentrations and Pharmacokinetic Parameters Following a Multiple Dosing (8x240 mg) of Verapamil HCl ER 120 mg Tablets
(N=27)

Time hr	Treatment A Mylan Lot #2B006H ng/mL (CV)	Treatment B Isoptin® Lot #20900074 ng/mL (CV)
0	0.00	0.00
120	66.86 (36.5)	63.29 (37.9)
144	60.29 (34.6)	60.09 (41.3)
168	61.65 (34.7)	60.55 (36.3)
168.5	61.78 (35.4)	60.10 (37.5)

169	70.82 (31.3)	68.13 (37.9)
169.5	81.67 (27.1)	80.29 (37.1)
170	93.67 (23.9)	94.86 (37.3)
170.5	108.06 (23.4)	105.40 (32.4)
171	123.38 (24.6)	123.45 (33.4)
172	144.74 (22.8)	148.13 (29.0)
173	160.27 (23.9)	166.17 (30.8)
174	171.49 (22.5)	178.20 (27.4)
175	170.28 (20.9)	171.95 (25.5)
176	164.49 (19.1)	168.83 (24.5)
178	149.58 (19.6)	152.06 (23.4)
180	126.51 (20.9)	129.44 (24.9)
184	88.70 (31.0)	90.10 (31.3)
192	64.18 (39.0)	63.18 (37.2)

			90% CI
AUC(0-24)(ng.hr/mL)	2677.1 (21.2)	2715.6 (25.9)	
Cpeak (ng/mL)	177.2 (20.9)	182.6 (26.6)	
Cmin (ng/mL)	58.9 (34.6)	56.9 (35.0)	
Tpeak (hr)	174.3	174.2	
Css (ng/mL)	111.5 (21.2)	113.2 (37.2)	
Fluct1 (%)	108.1 (27.9)	113.3 (27.3)	
Fluct2 (%)	227.0 (47.7)	249.3 (45.7)	

LnAUC(0-24) 95-104%
LnCpeak 92-103%
*Fluct1 = (Cpeak-Cmin)/Css*100
**Fluct2 = (Cpeak-Cmin)/Cmin*100
Cmin = Min. Conc. from time range 168-192 hours
Css = AUC/24

1. The plasma verapamil and norverapamil levels peaked at 174 hours for both the test and the reference products.

2. An analysis of steady-state attainment was performed using Cmin data from the 120, 144 and 168 hours plasma samples. Regression analysis of these data showed that no statistically significant differences in slopes between treatments exist for either verapamil or norverapamil.

3. For verapamil, the least squares means for AUC(0-24) and Cpeak values were 1.4% and 5.6% lower, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for each of the above parameters are within the acceptable range of 80-125%.

4. For norverapamil, the least squares means for AUC(0-24) and Cpeak values were 1.6% and 3.2% lower, respectively, for the test product than for the reference product. The differences were not statistically significant. The 90% confidence intervals for AUC(0-24) and Cpeak are within the acceptable range of 80-125%.

5. Additional analysis of variance was performed by the reviewer using the following model

Y = SEQ SUBJ(SEQ) PER TRT; (whereas period = 3)

was employed in the statistical analysis of the study, resulted in the following 90% confidence intervals for LnAUC(0-24) and LnCpeak of

Verapamil

LnAUC(0-24)	93.9-105.9%
LnCpeak	88.5-104.6%

Norverapamil

LnAUC(0-24)	94.9-104.2%
LnCpeak	92.2-103.1%

The 90% confidence intervals for the above pharmacokinetic parameters calculated using the above model are within the acceptable range of 80-125%.

6. Systolic and diastolic blood pressure, heart rate and percent change from baseline of the EKG PR interval were analyzed for statistical differences. There were no clinically significant differences in the parameters evaluated.

IX. Formulation:

Mylan's formulation for its verapamil HCl ER 120 mg tablet is shown below:

Verapamil HCl Extended-Release Tablet 120 mg

	MG Per Tablet
Active Component	
Verapamil HCl, USP	120.0
Inactive Components	
Povidone, USP	

Purified Water, USP	
Sodium Alginate NF	
Microcrystalline Cellulose NF	
Magnesium Stearate/ Sodium Lauryl Sulfate	
Total	350.0

Inactive Components (Film-Coat)

Blue . Coating Suspension	
Solids Contribution**	12
Average Target Film Coat Weight	12
Total Theoretical Weight	362.0

* The Blue . Coating Suspension Purified Water, USP which is added as a processing aid but does not contribute to the weight

** Solids consist of hydroxypropyl methylcellulose, polydextrose, titanium dioxide, triacetin, polyethylene glycol, and FD&C Blue #1 Aluminum Lake

[1] Purified Water, USP is added to the product as a processing aid but does not contribute to the total weight, therefore, Purified Water, USP quantities are expressed parenthetically.

X. In vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL of Simulated Gastric Fluid T.S (no enzyme) for one hour, then Simulated Intestinal Fluid T.S. (no enzyme) for 2, 3.5, 5 and 8 hours.
Number of Tablets:	12
Test Product:	Mylan's Verapamil HCl ER tablets, 120 mg Lot #2B006H
Reference Product:	Knoll's Isoptin® SR tablet, 120 mg lot #20900074.

The dissolution testing results are presented in Table VII.

XI. Comments:

1. The firm's single-dose bioequivalence study #Vera-9523a under fasting conditions, conducted on its 120 mg verapamil HCl ER tablet is acceptable. The two study drugs did not differ significantly with respect to mean values for any of the pharmacokinetics parameters. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and Cpeak are within the acceptable range of 80-125% for verapamil and norverapamil.

2. The firm's single-dose bioequivalence study #Vera-9578 under fasting and nonfasting conditions, conducted on its 120 mg verapamil HCl ER tablet is acceptable. The ratios of the test mean to the reference mean for AUC(0-t), AUCinf and Cpeak are within the acceptable range of 0.8-1.2 for verapamil and norverapamil under nonfasting conditions.

3. The firm's multiple-dose bioequivalence study #Vera-9579 under fasting conditions, conducted on its 120 mg verapamil HCl ER tablet is acceptable. The 90% confidence intervals for LnAUC(0-24) and Cpeak are within the acceptable range of 80-125% for verapamil and norverapamil.

4. The in vitro dissolution testing for the test product 120 mg verapamil HCl ER tablets is acceptable.

XII. Recommendations:

1. The single-dose bioequivalence study #Vera-9523a, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended Release 120 mg Tablets, lot #2B006H, comparing it to Isoptin^{R} SR 120 mg Tablets manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Verapamil HCl Extended Release 120 mg Tablets is bioequivalent to Knoll's Isoptin^{R} SR 120 mg Tablets.

2. The single-dose post-prandial bioequivalence study #Vera-9578, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended Release 120 mg Tablets, lot #2B006H, comparing it to Isoptin^{R} SR 120 mg Tablets manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's Verapamil HCl Extended Release 120 mg Tablets is bioequivalent to Knoll's Isoptin^{R} SR 120 mg Tablets.

3. The multiple-dose steady-state bioequivalence study #Vera-9579, conducted by Mylan Pharmaceuticals Inc., on its Verapamil HCl Extended Release 120 mg Tablets, lot #2B006H, comparing it to Isoptin^{R} SR 120 mg Tablets manufactured by Knoll Pharmaceuticals, has been found acceptable by the Division of Bioequivalence. The

study demonstrates that Mylan's Verapamil HCl Extended Release 120 mg Tablets is bioequivalent to Knoll's Isoptin^{R} SR 120 mg Tablets.

4. The dissolution testing conducting by Mylan Pharmaceuticals Inc., on its verapamil HCl ER 120 mg Tablets, lot #2B006H is acceptable. The dissolution testing should be conducted in 900 mL of simulated gastric fluid without enzyme (first hour) and 900 mL of simulated intestinal fluid without enzyme (second hour and thereafter) at 37^{0}C using USP 23 apparatus II (paddle) at 50 rpm. Based on the submitted data the following tentative specifications are recommended:

1	hour
2	hours
3.5	hours
5	hours
8	hours

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATR

Date: 10/7/96

Concur: _____ Date: 10/7/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/10-4-96 wp 74587SD.496
cc: ANDA #74-587, original, HFD-658 (Makary), Drug File, Division File.

Table VII In Vitro Dissolution Testing

Drug (Generic Name):Verapamil ER
Dose Strength: 120 mg Tablets
ANDA No.:74-587
Firm: Mylan Pharmaceuticals Inc.
Submission Date: April 4, 1996
File Name: 74587SD.496

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium:900 mL SGF for 1 hour, then SIF
Specifications:
Reference Drug: Knoll's Isoptin SR tablets, 120 mg
Assay Methodology·

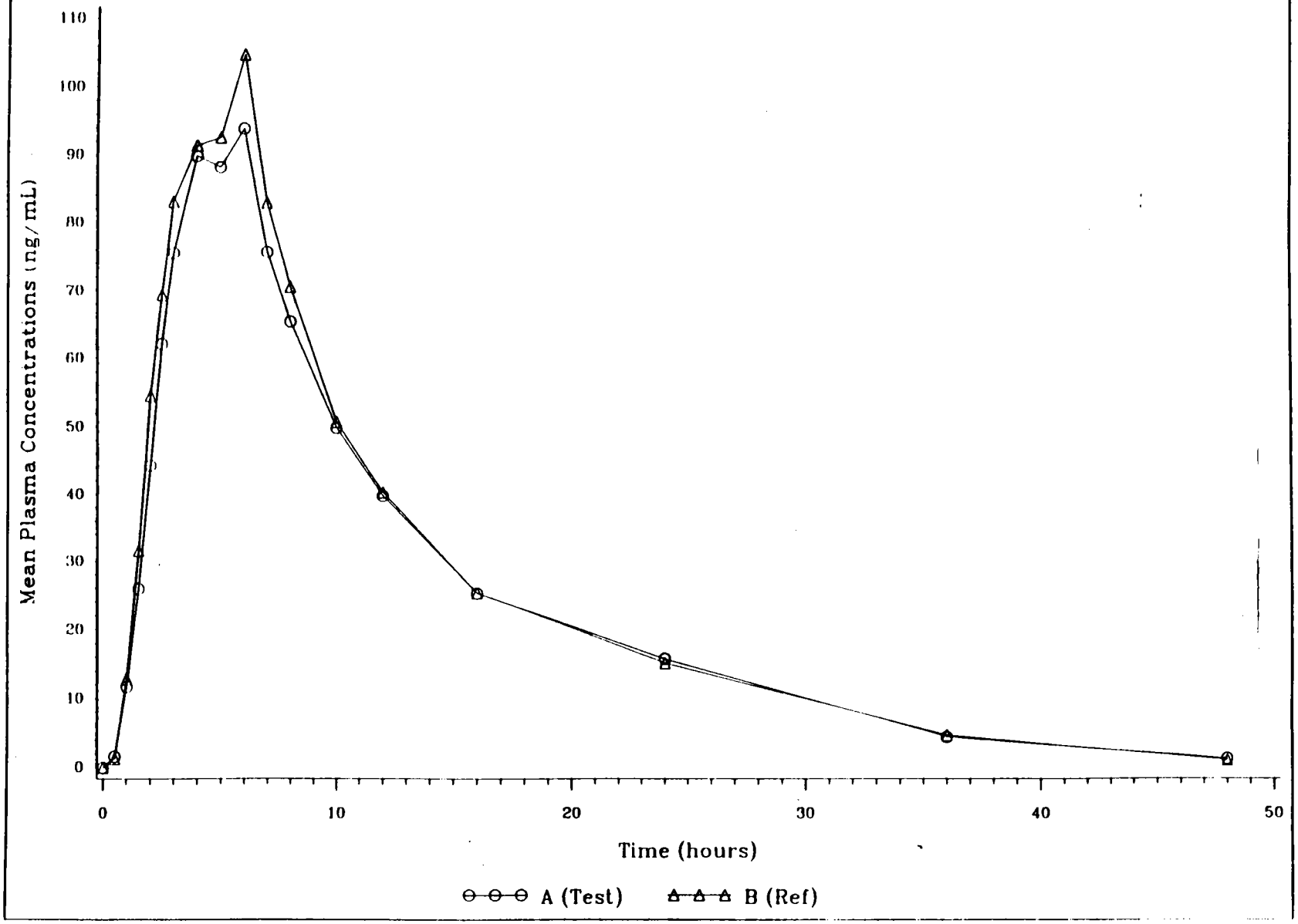
II. Results of In Vitro Dissolution Testing:

Sampling Times (hr)	Test Product Lot #2B006H Strength(mg) 120			Reference Product Lot # 20900074 Strength(mg) 120		
	Mean %	Range	%CV	Mean %	Range	%CV
1	20		2.5	14		10.2
2	29		4.0	24		7.8
3.5	46		7.7	41		11.0
5	68		8.3	72		8.6
8	98		4.7	102		2.5

VERAPAMIL (VERA-9523a)

Total Dose: 2 x 120mg Tablet, Study Type: Fast

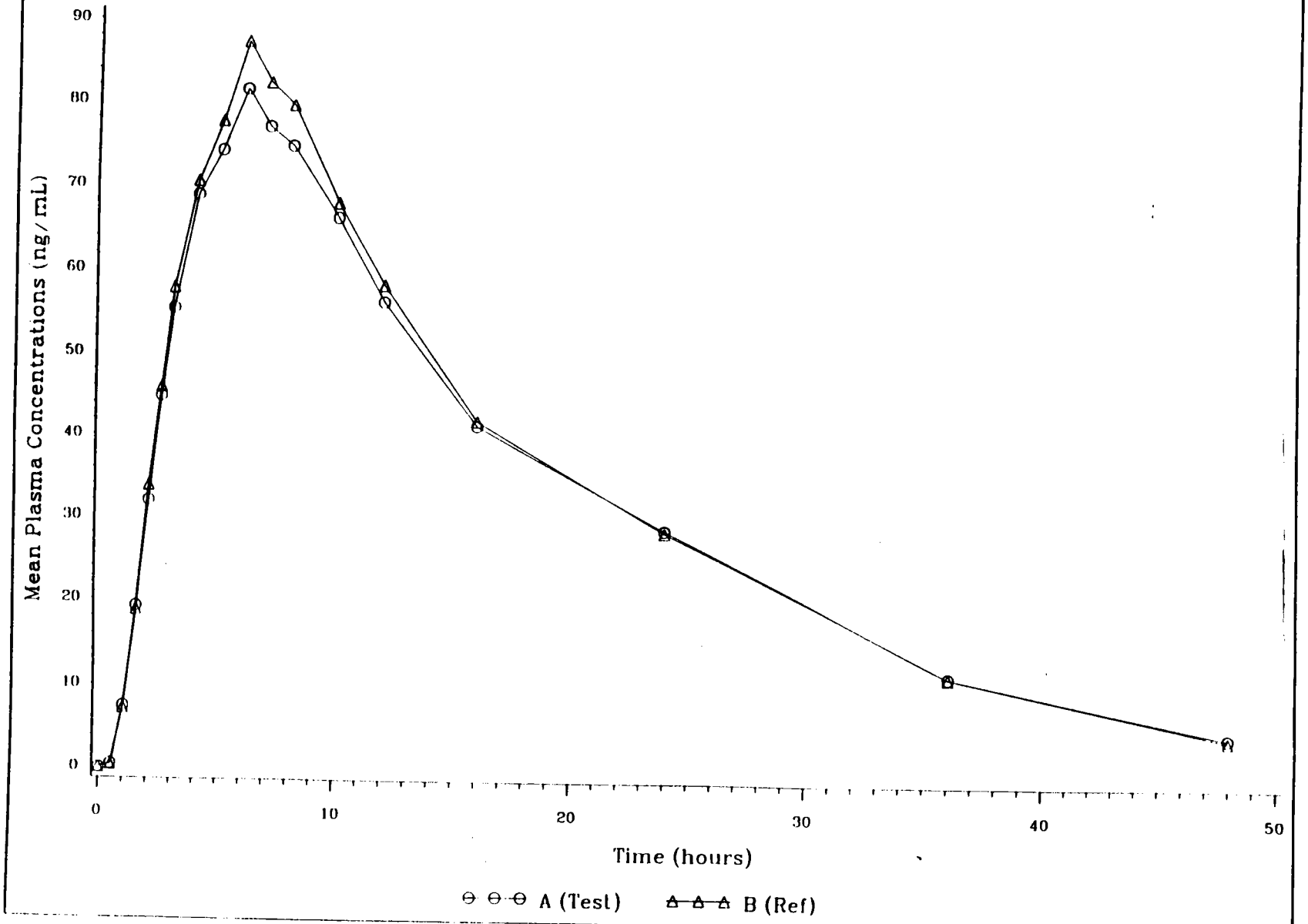
Mean Verapamil Plasma Concentrations



VERAPAMIL (VERA-9523a)

Total Dose: 2 x 120mg Tablet, Study Type: Fast

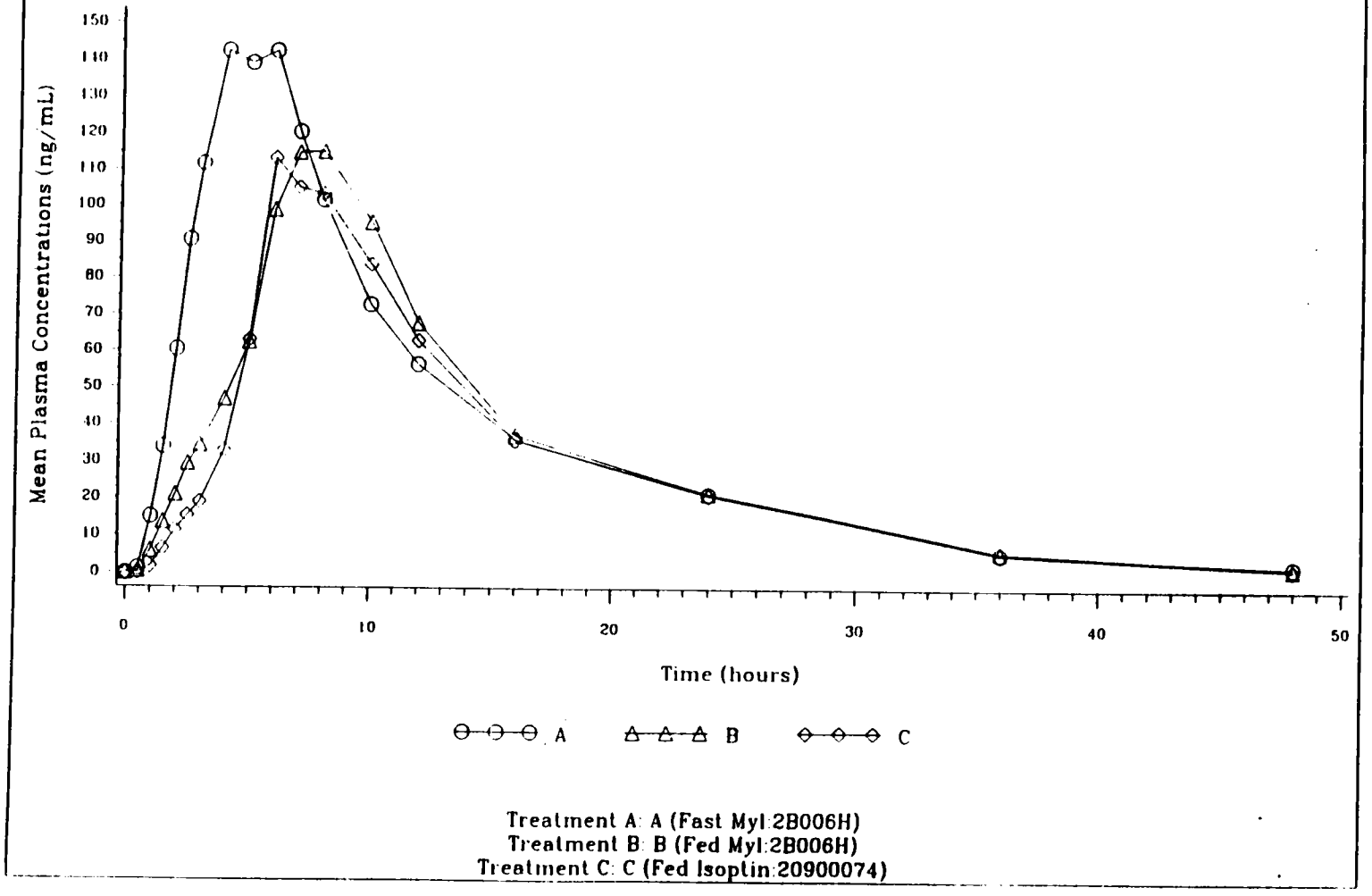
Mean Norverapamil Plasma Concentrations



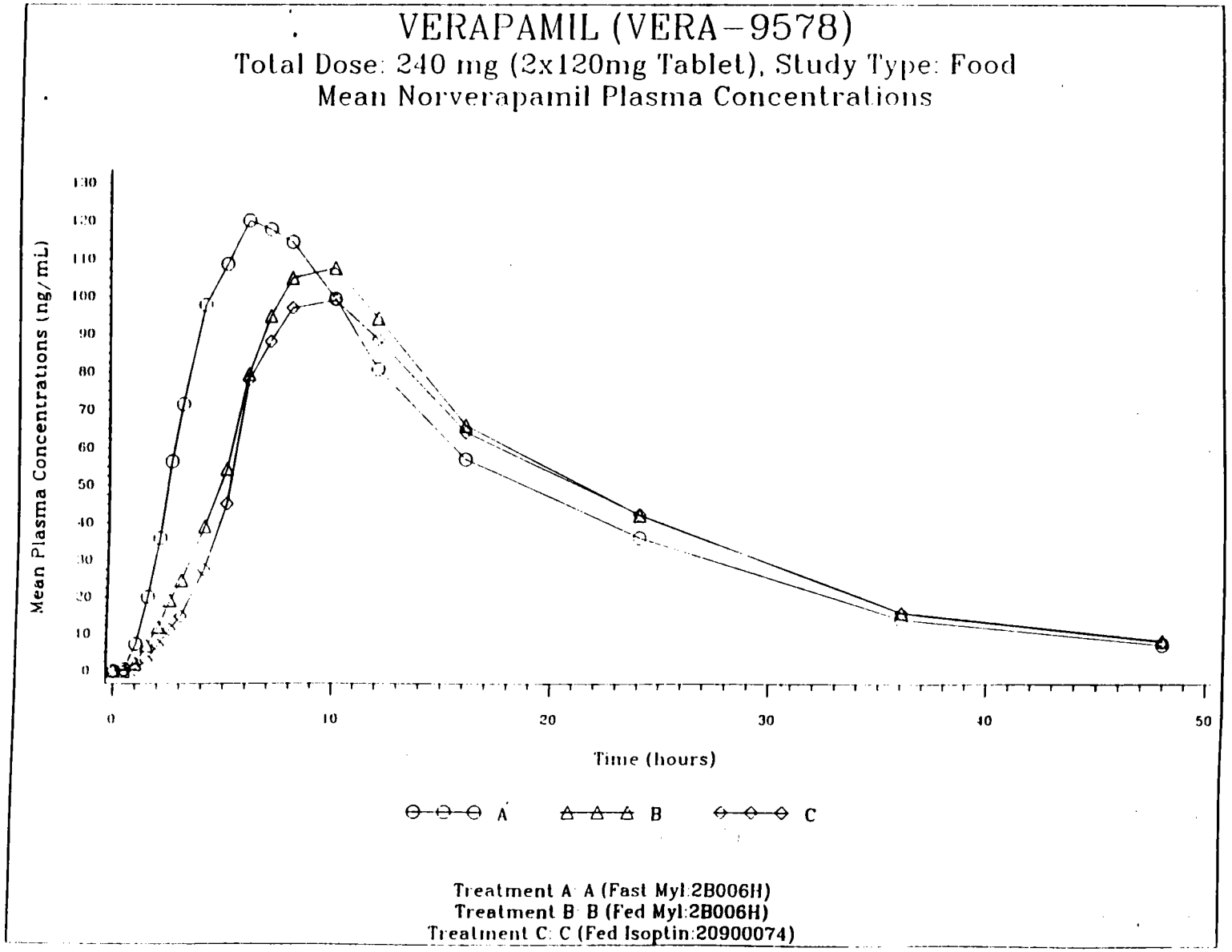
VERAPAMIL (VERA-9578)

Total Dose: 240 mg (2x120mg Tablet), Study Type: Food

Mean Verapamil Plasma Concentrations



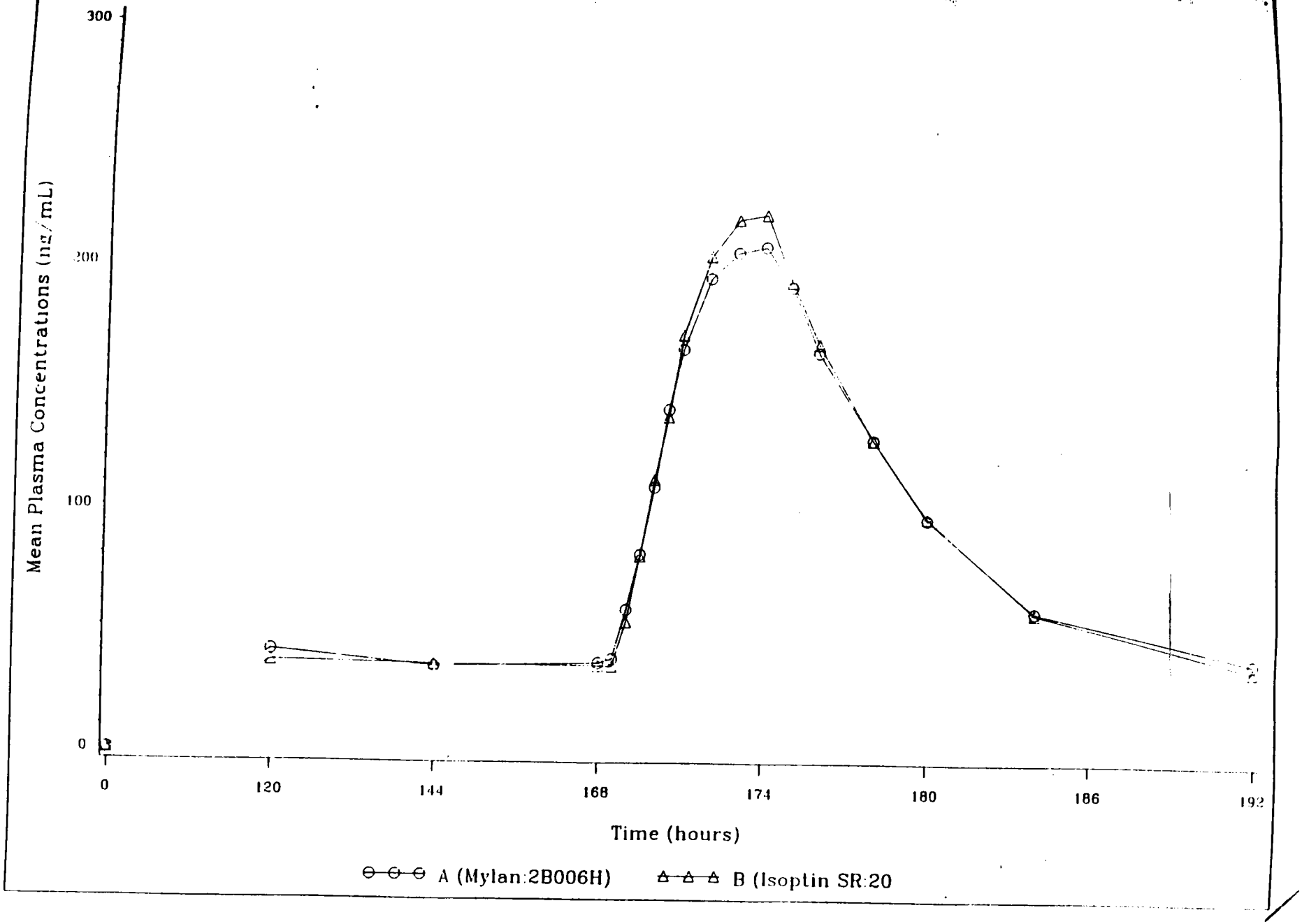
Treatment A: A (Fast Myl:2B006H)
Treatment B: B (Fed Myl:2B006H)
Treatment C: C (Fed Isoptin:20900074)


VERAPAMIL (VERA-9578)
Total Dose: 240 mg (2x120mg Tablet), Study Type: Food
Mean Norverapamil Plasma Concentrations
Mean Plasma Concentrations (ng/mL)
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
Time (hours)
A
B
C
Treatment A: A (Fast Myl:2B006H)
Treatment B: B (Fed Myl:2B006H)
Treatment C: C (Fed Isoptin:20900074)

VERAPAMIL (VERA-9579)

Total Dose: 240 mg 2x120mg Sustained Release Tablet Study Treatment

Mean Verapamil Plasma Concentrations



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ATTACHMENT 1

VERAPAMIL (VERA-9579)

Total Dose: 240 mg (2x120mg x 8 days) Tablet, Study Type: Steady State

Mean Norverapamil Plasma Concentrations